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Tuberous sclerosis clinical factors in long term outcome

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TUBEROUS SCLEROSIS
CLINICAL FACTORS IN LONG TERM OUTCOME

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SUMMARY

Tuberous sclerosis (TSC) is a dominantly inherited disorder with a high spontaneous mutation rate and a birth incidence of 1 in 10,000. It is a systemic disorder characterised by the growth of hamartomas, which in turn give rise to the clinical manifestations, for example, epilepsy and learning difficulties. Although some patients with TSC are only mildly affected and lead a normal life with typical life expectancy, there is an immense amount of morbidity associated with this disease. In addition, for the majority of patients there is reduced life expectancy. The purpose of this thesis is to look at the clinical factors that contribute to the morbidity and mortality seen in TSC and examine means of reducing the impact of these factors on long-term outcome. It reports a longitudinal population study of a small but defined group of patients looking at the epidemiology and natural history (the morbidity and mortality) suffered by in this population. It investigates the current treatment regimes for the types of epilepsy (infantile spasms and non-convulsive status epilepticus) known to be associated with the highest risk of learning difficulties in order to determine the most efficacious treatment for the seizures potentially reducing long-term psychomotor delay. A cochrane review of the treatment of infantile spasms was performed. This thesis also examines the effect of exogenous melatonin on sleep disorders (one of the major causes of morbidity) in tuberous sclerosis and the natural circadian rhythms in patients with sleep disorder in TSC and compares them with the normal population. Two important causes of premature mortality in TSC patients are respiratory and renal failure. This thesis examines the prevalence and underlying causes of end stage renal failure in adults with TSC and reviews the literature of LAM (in patients both with and without TSC) investigating further the natural history and treatment of LAM in TSC.

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Statement of Authors Contribution

This thesis contains a combination of research techniques including the collection of epidemiology data, systematic reviews and original research.

Epidemiological data collection

Chapter two looked at the epidemiology, mortality and morbidity of the tuberous sclerosis (TSC) population in the Bath Health District. It involved the retrieval and examination of the relevant medical records and reports, scrutiny of the Bath TSC data base and examination of the individual patients when they attended clinic or were visited for other research projects. It was undertaken solely by the author (ECH).

Systematic reviews

There are several systematic reviews included in this thesis.

The first review undertaken by the author was looking at the use of steroids and ACTH in the treatment of infantile spasms. This was a simple review using a single database and only considering studies published in English, the second review looking at vigabatrin in the treatment of infantile spasms in patients with TSC used two databases but again only considered studies published in English. A third review searched the English literature for all cases of lymphangioleiomyomatosis again used two data bases. All three of these reviews were performed solely by ECH.

A fourth review was the cochrane review looking at the treatment of infantile spasms. This involved searching several databases, in all languages, corresponding with colleagues, authors and drug companies for which ECH was fully responsible and appeals at international conferences for which JPO was responsible. ECH was also responsible for developing the protocol design, the database of the studies, data collection and extraction, data analysis and presentation of the results. JPO and PM had joint responsibility for the protocol, data extraction and agreement of results.

Original research

The following pieces of original research have been included in this thesis;

1. The treatment of infantile spasms with high dose oral prednisolone. ECH was responsible for developing the study design, collecting eligible patients, retrieving

and reviewing the medical notes, extracting the relevant data, data analysis and presentation of the results.

2. The United Kingdom Infantile Spasms Study. This is a multicenter randomised trial looking at the treatment of infantile spasms. ECH was responsible, under JPO's supervision for developing the trial design, protocol and trial packs which were put to the trial steering committee for comment and approval. ECH remains closely involved with the trial as a member of the trial steering committee. Management of data, developmental assessment and analysis are the responsibility of another research fellow of Prof. Osborne, Dr Andrew Lux.
3. Oral treatment of non-convulsive status epilepticus in tuberous sclerosis. ECH was responsible for developing the study design, collecting eligible patients, retrieving and reviewing the medical notes, extracting the relevant data, data analysis and presentation of the results.
4. Lymphangioleiomyomatosis and tuberous sclerosis: patient ascertainment. ECH was responsible for developing the study design, recruiting patients, retrieving and reviewing the medical notes and examining the patients (with the exception of three patients (who were seen by Sue Thompson) extracting the relevant data, data analysis and presentation of the results.
5. End stage renal failure in adults with the tuberous sclerosis complex. ECH was responsible for reviewing the results and writing up the data for this study. The study design, data collection and initial assessment were done by Dr Antonia Clarke.
6. The effect of melatonin dosage on the sleep disorder in tuberous sclerosis. ECH was responsible for developing the study design, including the diaries for data collection, recruiting patients, data analysis and presentation of the results.
7. Melatonin excretion in normal children and tuberous sclerosis with sleep disorder responsive to melatonin. ECH was responsible for developing the study design, including data collection forms, recruiting eligible patients and controls, data analysis and presentation of the results.

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I would like to thank all the following people for their valued contributions, which have made this research possible:

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Chapter Two

Professor John Osborne and Mrs Julia Legh-Smith for allowing me to use their data-base on the patients with Tuberous Sclerosis in the Bath region.

Chapter Four – The United Kingdom Infantile Spasm Study

Professor John Osborne, Dr Richard Appleton, Dr Colin Kennedy, Dr Richard Newton, Dr Finbar O'Callaghan, Dr Christopher Verity and Dr Lisa Vickers who formed the core group which was responsible for approving the design of the trial protocol and for obtaining funding. Formal statistical input into the study design was given by, Dr Anthony Johnson.

Professor John Osborne, Dr Stuart Edwards, Dr Anthony Johnson, Dr Colin Kennedy, Dr Andrew Lux, Dr Richard Newton, Dr Finbar O'Callaghan, and Dr Christopher Verity who formed the Trial Steering Committee which was responsible for approving the design of the trial packs, recruiting centres to participate in the trial and obtaining ethical approval.

Chapter Five – Cochrane Review on the Treatment of Infantile Spasms

Professor John Osborne and Professor Phillip Milner who agreed and approved the review at all stages and independently evaluated which studies should be included and excluded from the review and also independently extracted data from the included studies.
Dr Tony Marson and the Cochrane Group for all their advice.

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Professor Frank Besag for his idea of trying oral diazepam to terminate non-convulsive status in patients with Tuberous Sclerosis.

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Chapter Eight – Renal Disease

Dr Antonia Clarke, Dr Christopher Kingswood and Prof. John Osborne who designed the questionnaire, identified the members of the European Dialysis and Transplant Association, distributed and collected the questionnaires.

Chapter Nine – Sleep Disorder in Tuberous Sclerosis

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CHAPTER ONE

TUBEROUS SCLEROSIS

Introduction

Tuberous sclerosis (TSC) is a dominantly inherited disorder with a high spontaneous mutation rate and a birth incidence that may be as high as 1 in 10,000[1]. It is now known to be a systemic disorder characterised by the growth of benign tumours (hamartomas), which may arise in almost any organ of the body with the possible exceptions of striated muscle, the peripheral nerves, the meninges and the thymus gland. Although TSC is an inherited disorder it may not always manifest in childhood and clinical features may develop at any age. The severity of the disease varies considerably, not only between individuals but also within families. This makes genetic counselling particularly difficult as a mildly affected parent with normal intellect is at risk of having an affected child who may either be mildly affected or have severe learning difficulties, extreme behavioural problems and refractory epilepsy.

Over the past century and a half our knowledge of the clinical manifestations and the natural history of this condition has increased substantially. Whereas TSC was thought to be exceptionally rare, causing severe handicap and early demise, it is now known to be relatively common, affecting patients in a wide variety of ways, although it is still associated with a high incidence of morbidity and mortality. It is, therefore, imperative that clinicians continue to improve their understanding and treatment of this condition, not only to maximise longevity but also to allow individuals to achieve their maximum potential.

The very first reference to TSC is probably the illustration drawn by Pierre Rayer in 1835 representing the facial angiofibroma (see figure one) of TSC. Von Recklinghausen gave the first description of TSC in 1862 when he described sclerotic areas in the brain and cardiac rhabdomyomas in a stillborn child, who he thought had neurofibromatosis. In 1880 Bourneville named the condition after accurately describing the potato-like (tuberous) hard (sclerosis) cerebral lesions pathognomonic of the disease. Over the following decade dermatologists such as Balzer, Menetrier and Pringle made the association between the

facial rash and mental retardation in individuals found to have the cerebral lesions of TSC at post-mortem.

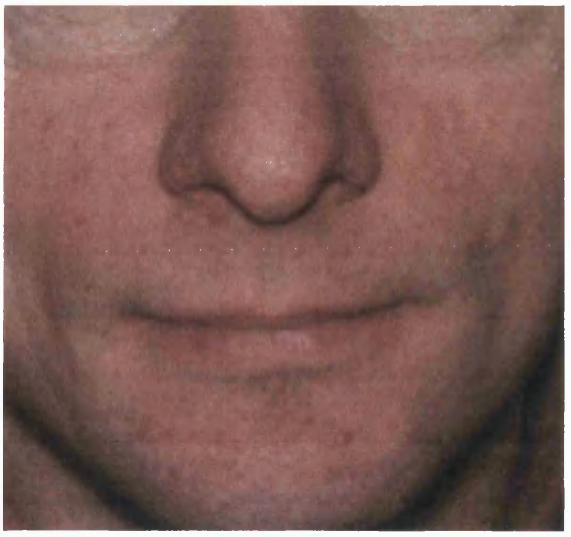


Figure one - angiofibroma

At the beginning of the 20th century pathologists had started to recognise other lesions associated with these tubers, in the heart, kidneys and skin and Vogt described the clinical triad of angiofibroma, severe epilepsy and mental retardation as a means of recognising TSC clinically in patients whilst alive; previously the diagnosis had only been able to be made posthumously. Unfortunately, this gave rise to the misconception that all three features had to be present for the diagnosis to be made, which not only led to under recognition of this disease but failure to recognise (and therefore to treat) the other complications of TSC. However, over the latter half of the past century it has gradually become apparent that the disease is more complex than that originally recognised and can affect almost any part of the body.

In 1920 Berg noted the hereditary nature of TSC and it was soon realised that some relatives had the skin lesions without the mental handicap and over the following decades, other manifestations of TSC have been documented. However it was not until Gomez's study in 1967 that it became clear that as many as half of affected individuals had normal intelligence and only one third had the complete Vogt's triad. This led Gomez[2] to publish a set of criteria in 1979, updated by Osborne in 1988[3], on which the disease could be recognised. These diagnostic criteria were divided into three groups.

Diagnostic criteria for the diagnosis of TSC[2,3]

Primary criteria
These are diagnostic of TSC even in the absence of any other stigmata of TSC

1. Angiofibroma
2. Retinal phakoma
3. Multiple subependymal nodules
4. Multiple cortical tubers
5. Forehead fibrous plaque
6. Shagreen patch

Diagnostic criteria with a first degree relative

1. Subependymal giant cell astrocytoma
2. Cardiac rhabdomyoma
3. Single cortical tuber
4. Single retinal phakoma

Secondary diagnostic criteria
These can occur in unaffected individuals but a combination of two or more implies a diagnosis of TSC because of the low risk of more than one occurring in an unaffected individual.

1. Hypomelanic patches
2. Bilateral polycystic kidneys
3. Lymphangioleiomyomatosis of the lung
4. Cardiac rhabdomyoma
5. Renal angiomyolipoma

In 1998 the clinical diagnostic criteria were revised once more by the Tuberous Sclerosis Complex Consensus[4], yet again reflecting the increasing knowledge and understanding of this disorder. It had become apparent that some features previously thought to be pathognomonic of the disease, for example cortical tubers could occur in patients without TSC, as could renal angiomyolipoma and lymphangioleiomyomatosis. It was also known that when these individuals had no other signs of TSC, they did not have children who inherited the disorder. Studies of families with a known gene mutation also showed that where an individual had a disease causing mutation, they always had convincing signs of the disorder and that those with no signs were always unaffected. Penetrance was therefore high. The only reclassification in UK families following more traditional analysis involved individuals with one possible hamartoma – usually white patches or a single ungula fibroma. Improving the criteria required for diagnosis, would also highlight the potential complications of the disease to the clinicians at the time of diagnosis, hopefully improving long-term follow up and reducing morbidity and mortality from the disease. It was therefore decided;

"A definite diagnosis of TSC should be reserved for patients with two or more distinct types of hamartomas rather than multiple lesions of the same type in the same organ system" [4]

For the purpose of this definition renal angiomyolipoma and pulmonary lymphangioleiomyomatosis are considered as one hamartoma since some individuals with these two hamartomas but without other signs of TSC do not pass TSC onto their children. It is likely that the clinical criteria for TSC will become less important with the discovery of two genes for TSC: it is probable that diagnosis by genetic testing will be available for the vast majority of individuals in the near future: it is already possible for up to 70% of individuals in the best laboratories.

The diagnosis of TSC was also made easier (and is often made at an earlier age) as the result of the introduction of new imaging techniques particularly computerised tomography (CT) (1973) and magnetic resonance imaging (MRI) (1980's). Before such techniques were available TSC could often only be recognised clinically if the patient developed the skin lesions that are pathognomonic of TSC, for example angiofibroma and shagreen patches, or became symptomatic from the hamartomas, for example developed seizures, haematuria, or pneumothoracies. With the advent of CT, MRI etc it has become apparent that hamartomas may be present in many organs e.g. brain and kidney without giving rise to symptoms. For example, it is now known that the vast majority of patients with TSC have subependymal calcifications (within the brain) that are easily recognisable on CT scan, are present from birth (but may only calcify in the first year of life) and rarely occur in the absence of TSC. Before CT scanning was available, if an affected individual had a child, or if for example a child developed infantile spasms, only a skull X-ray or air encephalogram could be undertaken to look for intracranial lesions. It is also possible to perform echocardiography to look for rhabdomyomas: a positive finding would help confirm the diagnosis but a negative finding would not help exclude the diagnosis. Only 30 –50% of TSC patients have rhabdomyomas at birth and they often regress over the first few months of life. Likewise ophthalmology confirmation of a retinal phakoma would help substantiate the diagnosis, but they are not present in all patients. Nowadays a CT brain scan can be undertaken; if subependymal nodules are present it is highly probable that the child has TSC. Unfortunately, even with these more advanced imaging techniques, it is not always possible to make a definitive diagnosis of TSC. Other conditions such as neurofibromatosis type one and some congenital infections can give rise to calcification on imaging and grey matter heterotopia (including an autosomal dominant variant associated with epilepsy) can give an appearance similar to the non-calcified lesions seen in TSC.

Similarly, many patients with TSC have cysts and/or angiomyolipomas in their kidneys but only some have symptoms such as pain or bleeding. Ultrasound scan is a non-invasive but useful tool for diagnosing these lesions and in combination with other scanning techniques may help to make a diagnosis in a patient who has few clinical manifestations of TSC, but it can mislead: "AML" may not be found on further investigation. Renal cysts can also be found in normal individuals, it is estimated that approximately 1 in 40 people at 40 years of age will have one or more renal cysts.

Note: the majority of the cutaneous manifestations of TSC are not present at birth and may not develop until adulthood or rarely may never develop at all.

Genetics

Berg first noted the hereditary nature of TSC in 1920 and it was then recognised to be an autosomal disorder by Gunther and Penrose in 1935. However, the condition has a high spontaneous mutation rate accounting for about 60% of affected individuals[5]. A gene locus was discovered on chromosome **9q34** (TSC1) by Fryer[6] in 1987, but it soon became apparent that a second gene existed. This was located, by linkage studies, on chromosome **16p13** (TSC2) in 1992 by Kandt[7], and was cloned a year later by Nellist[8] who found that the TSC2 gene lies close to the PKD1 gene. The TSC1 gene was cloned in 1998 by Young et al[9]. The exact functions of the two gene products, hamartin (TSC1) and tuberin (TSC2) are still being researched but both are thought to act as tumour suppressor genes.

A number of tumour suppressor genes are now recognised and molecular studies have shown them to play an important role in the regulation of the normal cell cycle. For a tumour suppressor gene to exert a pathological influence on a cell, both alleles must be inactivated; the Knudsen[10] two hit theory explains why inheriting a defective copy of a tumour suppressor gene leads to an individual with multiple tumours. Normally for a tumour to arise (in an individual without an inherited or early embryonic defect), two independent somatic mutations are required, explaining why sporadic tumours can occasionally arise in a single tissue later in life. But, individuals who have already inherited an inactivated tumour suppressor gene only need one further somatic mutation to lose both alleles explaining why in TSC the tumours often occur earlier (as early as in utero) and tend to be multiple. This may also explain why clinical expression is extremely variable even within families, if chance affects the number and timing of second hits. The hypothesis that TSC genes were tumour suppressor genes was developed following the demonstration of loss of part of the normal gene in the hamartomas of individuals with TSC – a phenomenon known as loss of heterozygosity.

The TSC1 gene is 8.6kb in length and codes for a protein of at least 1164 amino acids called **hamartin**. The TSC2 gene is larger in size, 45kb in length and codes for a similar sized protein, **tuberin**, 1807 amino acids in length. Both proteins have regions similar in structure to the GTPase-activating proteins (GAP) human GAP3 and murine GAP. GTP is an energy source required for normal cell growth. GTPase-activating proteins break down GTP to GDP, an inactive form, thus inhibiting normal cell growth. It is therefore

postulated that hamartin and tuberin have a comparable effect to GAP proteins i.e. act as a growth suppressor gene. Consequently, if either hamartin or tuberin are deficient or do not function correctly there is uninhibited cell growth thus giving rise to the hamartomas seen in TSC.

Defects in either gene produce a remarkably similar phenotype, so that at present it is not possible to clinically detect which gene is affected in any affected individual, except in the rare cases where there is also early onset polycystic kidney disease (PKD) due to a deletion on chromosome 16 affecting both the TSC2 and the PKD gene[7]. However, there have been recent suggestions that TSC2 mutations may be seen more commonly in sporadic cases of TSC and may be associated with more severe handicap than TSC1 mutations, but further research is required in order confirm this hypothesis.

The rapidly increasing knowledge and understanding of molecular genetics may be beneficial in aiding diagnosis in this group of patients, but it also introduces new dilemmas. Pre-natal diagnosis is now available for families where a disease causing mutation has been identified but there is no reason to believe that the test will be able to predict the severity of affected individuals. This can lead to increased anxiety when choosing whether or not to opt for pre-natal testing and subsequent termination of an affected foetus. If the family opt for pre-natal testing, the mutation must be identified before the pregnancy and counselling given with preferably both partners together. Pre-natal testing can also be considered in subsequent pregnancies in individuals with apparent new mutations because of the risk of gonadal mosaicism even though the recurrence risk is less than about 2%. There is also then the dilemma of whether and when to test apparently unaffected individuals within a family. If found to be affected, not only can this be a constant source of worry in itself but it can also have financial implications, making it difficult, for example to acquire life insurance or a mortgage. On the other hand the individual may not want to risk having an affected child, and may opt to be tested as late in adult life as possible.

Prevalence

Earliest studies (Critchley and Earl[11] 1935 and Gunther and Penrose[12] 1935) investigating the prevalence and morbidity in TSC concentrated on small samples of institutionalised patients estimating TSC to be a rare disorder affecting 1 in 30 mentally handicapped

patients. Gunther and Penrose[12] also estimated 1 in 1,000 of the population to be handicapped giving a prevalence of TSC around 1 in 30,000. By the 90's, it was well known that TSC could present in a multitude of guises and not all sufferers had moderate or severe learning difficulties. Consequently several population-based prevalence studies were performed in the attempt to provide more accurate information. Unfortunately four of the studies involved only small numbers of patients: Wiederholt et al[13] 1985 gave a prevalence of 1 in 10,000 based on only eight patients; Umpathy[14] et al 1989 gave a prevalence of 1 in 34,000 based on 14 patients, Shepherd[15] et al 1991 a prevalence of 1 in 13,000 based on 12 patients and Ahlsen[16] et al 1994 a prevalence of 1 in 13,000 based on 32 patients.

The first epidemiological study to look at prevalence in different age groups was performed by Hunt and Lindenbaum[17] in 1984 reporting on 68 patients in the Oxford region giving an overall estimated prevalence of 1 in 30,000. They found decreasing prevalence with increasing age; 1:10,000 at birth, 1:15.000 under 5 years and 1:20,000 under 30 years of age. A further study carried out by Sampson et al in Scotland 1989[18] looked at 101 patients giving a similar overall prevalence of 1 in 27,000. In 1996 the largest population based study to date was published by Webb[19] et al totalling 131 known affected individuals from a population of 3,400,000 people, most of whom were examined for the review, unlike previous studies. They estimated a birth incidence of 1 in 10,000. They found only 40% of their patients to have learning difficulties giving a prevalence of 1 in 40,000 for TSC and severe learning difficulties, which is similar to that found by Gunther and Penrose[12].

Clinical manifestations

Cutaneous manifestations

1. Facial angiofibroma (figure one, page eight) affecting the cheeks, nasal folds and chin but often sparing the upper lip rarely occur before 2 years, but most often become apparent before adolescence and progressively increase in number and prominence. They are reported to occur in about 90% of patients with TSC. They result from proliferation of the normal dermal tissue with a vascular component giving rise to telangectatic nodules, while more fibrous lesions appear skin coloured. Either type may become pedunculated[20 21].

2. Shagreen patches (figure two) are usually found in the lumber region of the trunk and are a roughened raised area of skin, often slightly pigmented with a leathery consistency. They occur in 20-80%[21] of patients and vary considerably in size from a few inches to as much as a foot in diameter. They have an irregular edge. Some patients will have a number of smaller, so called "satellite" lesions either in isolation or surrounding a shagreen patch.

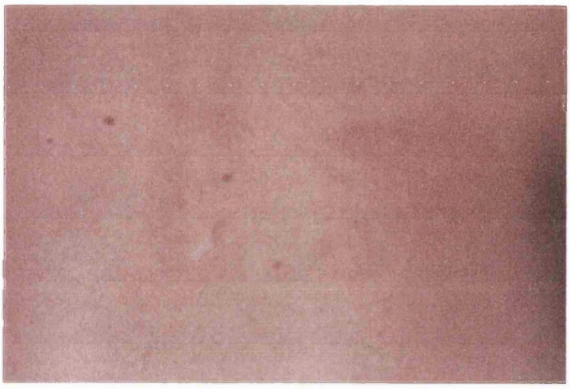


Figure two – Shagreen patch

3. Hypomelanic macules (figure three) are best seen with an ultraviolet light (Wood's light), are the commonest and often earliest skin sign of TSC, but are not unique to TSC and may occur in healthy individuals[3 20]. As a general rule the greater the number of hypopigmented patches the higher the risk of TSC, and the USA consensus conference[4] felt three was a significant number. Depigmentation may also affect the hair (known as poliosis – figure four) and iris, or occasionally causes a confetti type pattern (figure five) usually seen on the proximal limbs. Pathologically, there is an absence of melanosomes within a normal number of melanocytes (unlike vitiligo). It is not clear that these lesions are hamartomas.

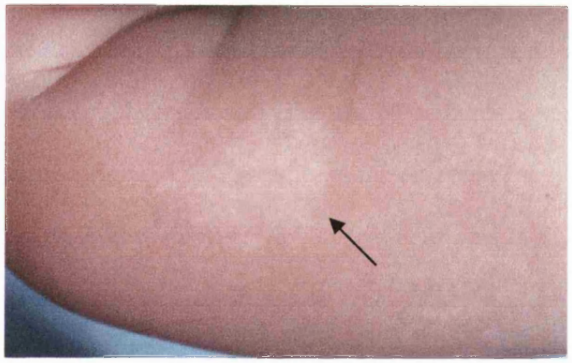


Figure three – Hypomelanic macule

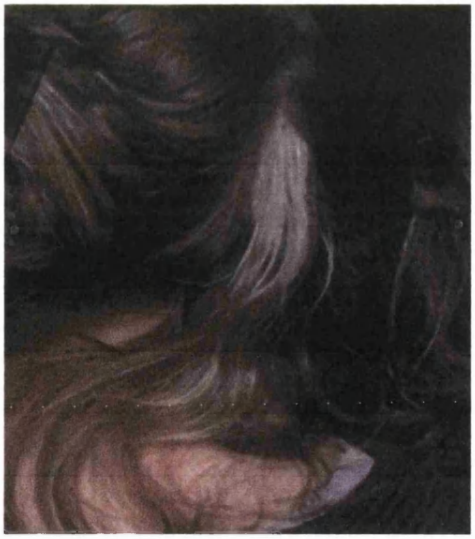


Figure four – Poliosis

Figure five – confetti depigmentation

4. Forehead fibrous plaques (figure six) are raised reddish areas of skin occurring on the forehead or scalp and occasionally the face. Unlike the shagreen patch, which has a roughened texture, these tend to have a smooth surface[3 21]. They may be the first skin signs of TSC. Histologically they are angiofibromatous.
5. Fibromas (figure seven) are flesh-coloured nodules commonly occurring in up to 70% of patients and may occur around the nails, more commonly the feet than the hands (ungual fibromas) or gums. They are a result of over proliferation of the dermal connective tissue and tend to re-grow after excision[3 21].

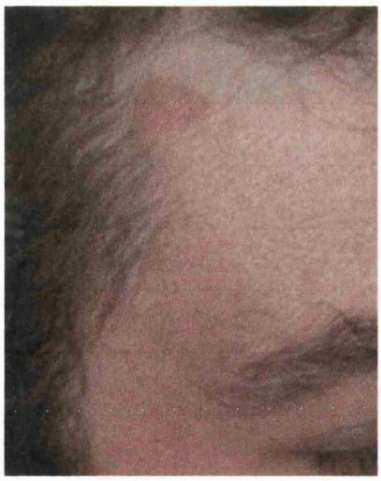


Figure six – Fibrous forehead plaque

Figure seven – Fibroma of nail

Pathological neurological manifestations

1. Cortical tubers (figure eight) are present in almost all cases of TSC and are traditionally shown on T2 weighted images but may be best visualised on flare sequence MRI scanning. Macroscopically, the tubers are prominent thickened gyri with an appearance not unlike a potato and they may feel hard (sclerotic), hence Bournville's description in 1880. Histologically they contain dysplastic cells resembling neurones and astrocytes[21]. The number and location of tubers varies widely and although it appears as though there is a relationship between the number of tubers, the risk of epilepsy and learning difficulties[22 23] this does not hold true for an individual. There may also be a correlation between position of the tubers and the clinical manifestations; for example, it has been suggested that there is a link between temporal lobe tubers and autistic tendencies[24].

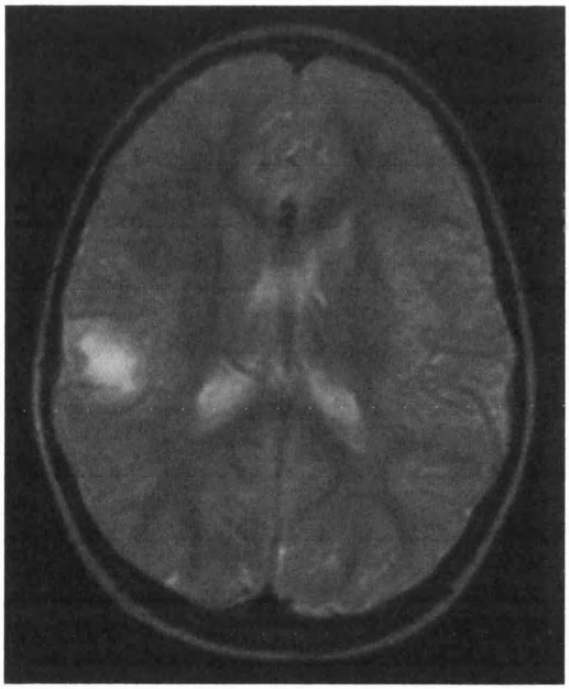


Figure eight – Cortical tuber (MRI FLAIR)

2. Subependymal nodules (figure nine) are best seen on CT imaging although they may be missed in the first few months of life before calcification takes place[3]. They range from small nodules to larger or multiple lesions, which may produce a candle-guttering effect[23] on the ventricular surface, and are nearly always but not universally present in all patients with TSC. Histologically they consist of a collection of giant astrocytes and look like giant cell astrocytomas, but many have calcified and do not grow.

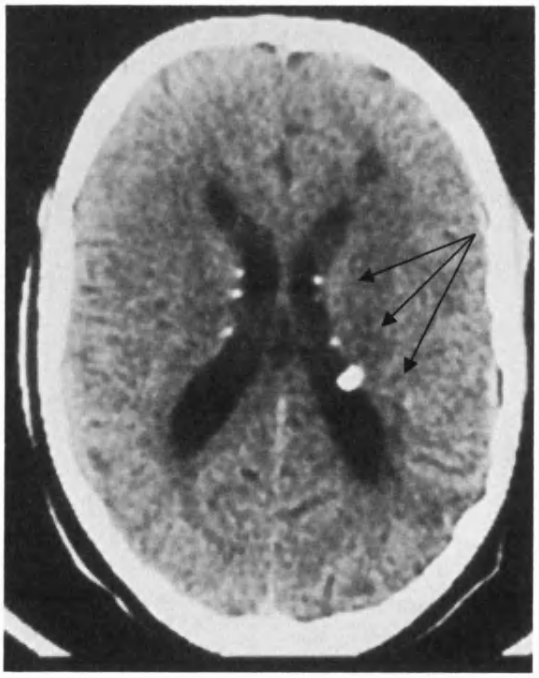


Figure nine – Subependymal nodules (CT scan)

Symptomatic neurological manifestations

1. Epilepsy (see later) is a common presenting feature in TSC affecting approximately 60%[19 25] of individuals most often beginning in the first two years of life, but can also occur in adults for the first time. Infantile spasms account for about half of the initial seizures with partial and generalised seizures making up the rest[26].
2. Severe learning difficulties (SLD) are seen in about 40% of patients[19 25] but rarely in the absence of fits[19 26]. Many are also lacking in verbal skills.
3. Behavioural problems are also common in these patients with hyperactivity, associated with poor sleep patterns and autistic behaviour predominating[27]. Self-injury is also seen.
4. Giant cell astrocytomas (figure ten) are much more common in TSC patients than the general population[28] and there is a continuing debate as to whether they arise de novo or from pre-existing subependymal nodules. They most commonly arise near to the Foramen of Munro and are essentially slow growing and benign but may lead to hydrocephalus and raised intracranial pressure if untreated. They commonly enhance with contrast injection on CT scan, unlike subependymal nodules, which do not often enhance[3]. However, if raised intracranial pressure does occur some larger subependymal nodules (usually >1-2cm) may enhance, leading to arbitrary radiological criteria to label such lesions as "GCA pre-symptomatically".

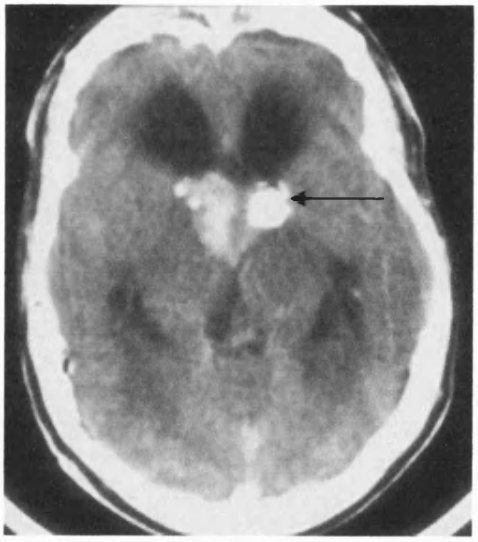


Figure ten – Giant cell astrocytoma (CT scan)

The kidney

1. Polycystic kidney disease (PKD) (figure eleven) is more common in patients with TSC than the general population. In these patients, the kidneys are bilaterally enlarged with

numerous cysts from birth and these patients require careful follow up through life as they commonly develop hypertension and chronic renal failure. Early onset PKD is linked to the TSC2 gene on chromosome 16[7] and has not been reported in patients carrying mutation in the TSC1 gene.

Figure eleven – Polycystic kidney (USS)

2. Angiomyolipoma (AML) (figure twelve) are highly vascular benign tumours consisting of smooth muscle and adipose cells occurring in 40-80%[29] of patients with TSC. They can occur at any age. Many patients remain asymptomatic but in others they may cause frank haematuria, pain, give rise to life threatening haemorrhage or occasionally cause renal failure.

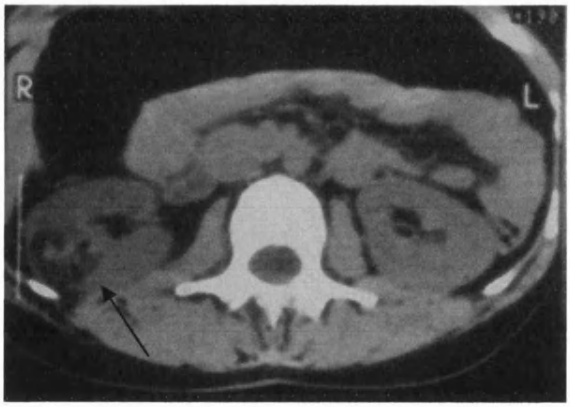


Figure twelve – Single renal angiomyolipoma (arrowed) (CT scan)

3. Cysts occur separately from PKD in approximately 30%[29] of patients with either TSC1 or TSC2. They may occur independently or coexist with AML. They may arise at any age and have been known to resolve spontaneously. They may give rise to similar problems as AML.
4. Renal cell carcinomas may be more common than in the general population, and are considered to arise de novo and not from pre-existing AML[29]. Their significance in TSC was highlighted by the discovery that the Eker rat (an animal model for renal cell carcinoma) has an inherited mutation in the rat TSC 2 gene[30].

The heart

1. Cardiac rhabdomyomas (figure thirteen) occur relatively frequently (30-50% of cases[21]) but rarely cause symptoms. If they do, it is usually in infancy when they can cause cardiac failure (and even death) from arrhythmia or obstruction. Unlike the other clinical manifestations of TSC that become more common with increasing age, these seem to shrink in size and even disappear with time, often disappearing rapidly, within weeks or months of birth. They can be demonstrated by echocardiography[3] and larger lesions may even be visualised in utero, usually in the third trimester. They can arise anywhere in the heart and may grow up to several centimetres in size as smooth but firm benign tumours. Histologically they are composed of large myocardial cells with large intracytoplasmic spaces[21].

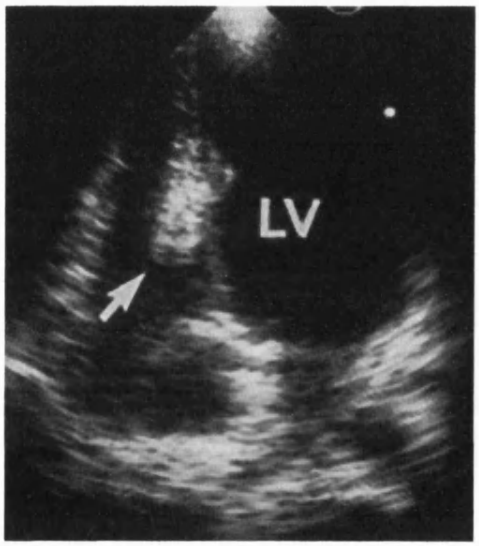
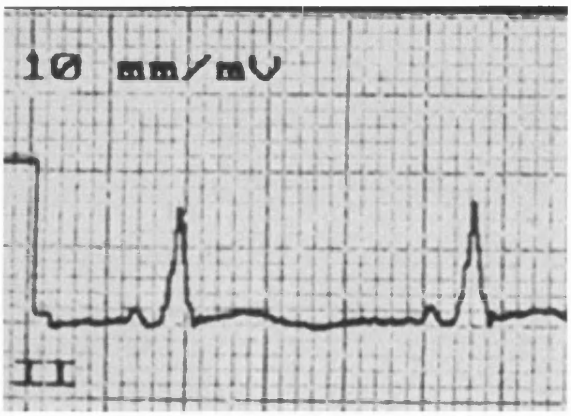


Figure thirteen – Cardiac Rhabdomyoma (Echo) (arrowed) in right ventricle. LV = left ventricle



1 large square = 0.2 sec

Figure Fourteen – WPW (ECG)

2. Wolff Parkinson White syndrome (WPW) can also occur in TSC, though it is rare. It has a typical electrocardiogram ECG pattern with a short PR interval and a wide QRS complex that begins as a slurred upwards deflection known as the delta wave (figure fourteen). WPW may predispose to supraventricular tachycardias, which in turn may lead to heart failure or sudden death.

The lung

Changes resembling pulmonary lymphangioleiomyomatosis (LAM) have been described as occurring in about 1% of TSC sufferers. LAM is a rare cystic lung disease (figure fifteen) that is usually considered generalised and progressive. It can be extremely difficult to treat and is generally considered to have a poor prognosis. It is almost exclusively reported to occur in women of childbearing age, the commonest presentation being dyspnoea and pneumothorax, after which many patients are thought to follow a relentless deterioration.

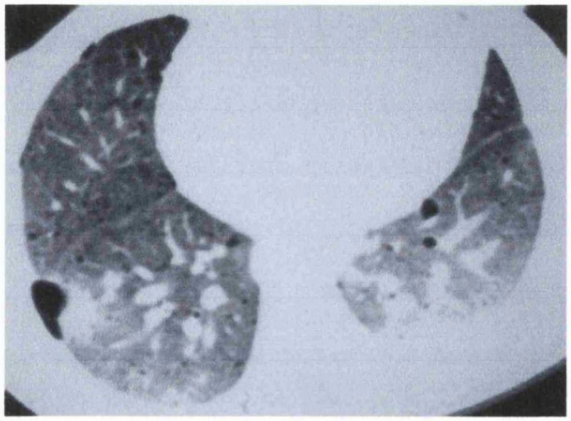


Figure fifteen– Lymphangioleiomyomatosis (HRCT)

The eyes

Retinal phakoma (figure sixteen) are benign astrocytomas arising from the retina. They often calcify with age but rarely cause problems unless they occur in the macular region.

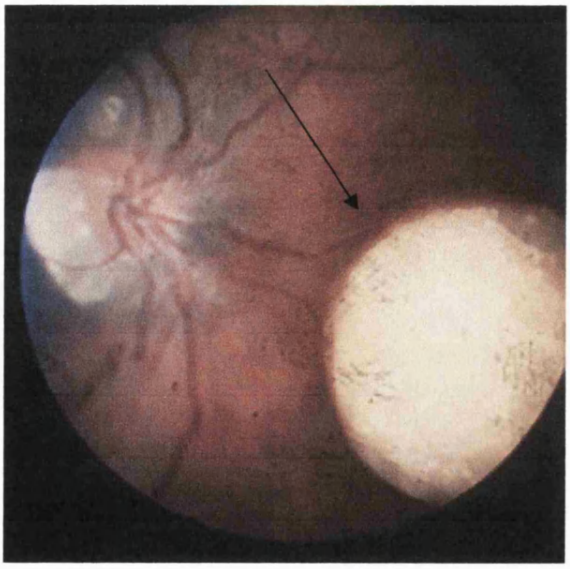


Figure sixteen – Retinal phakoma (fundoscopy) (arrowed)

The bones

Bony changes include cysts and sclerosis, but the incidence is unknown as they are usually asymptomatic.

Epilepsy

In its simplest form an epileptic seizure (fit or convulsion) can be defined as an abnormal paroxysmal electrical discharge of cerebral neurones. However, in reality epilepsy encompasses a vast array of clinical symptoms and signs with poorly understood underlying pathophysiology. As a consequence the many attempts to classify epileptic seizures and syndromes over the past century have often been confusing and misleading. The current classification, Commission on Classification and terminology of the International League Against Epilepsy[31] (ILAE), is based on the clinical manifestations of the seizures experienced together with findings from electroencephalogram (EEG) investigation and, whilst this classification does assist in communication between professionals in both the clinical and research setting, it is less helpful in determining the cause, prognosis or how the patient is best treated. It is likely that with time, as our understanding of the underlying pathophysiological processes that take place in epileptic seizures improves, particularly with regard to the chemical substrates involved, the classification will evolve and become more useful in determining which treatments are most likely to benefit the patient.

A further sub-classification divides epileptic seizures into three main groups; partial, generalised and unclassified. The first two groups are then further sub-divided. However this classification fails to make use of all the information available to physicians to describe epileptic seizures and a second classification has been devised by the ILAE[31]. This defines syndromes that are epileptic disorders characterised by a cluster of signs and symptoms occurring together, are often age related, may be inherited, and may have characteristic histories and results on investigation.

Although most types of epileptic seizures can occur in patients with TSC the most common are infantile spasms, partial seizures, tonic clonic seizures, and myoclonic seizures. Akinetic and drop attacks, status epilepticus and non-convulsive status epilepticus also occur in these patients. True three per second spike and wave absence seizures (previously called petit mal epilepsy) are very rare, probably arising in those with TSC only by chance.

It is probable that in TSC all seizure types are partial in onset (with many becoming rapidly secondarily generalised), with the cortical tubers acting as epileptigenic foci, whatever the seizure semiology. Even in infantile spasms it has been suggested by Curatolo[22] that the seizures may arise in one frontal lobe but spread so fast that ordinary EEG methods suggest the seizure arose in both hemispheres simultaneously.

Infantile spasms (also known as West's syndrome)

This is an age related epileptic syndrome, usually but not exclusively, comprising the triad; clinical manifestation of spasms, psychomotor retardation and hypsarrhythmia (see chapter three). The onset of spasms is almost exclusively during the first year of life with a peak between four and seven months. The spasms consist of a brief and sudden stiffening of the body. Most commonly there is flexion of the head, bending of the knees and abduction of the arms. However extensor spasms also occur as well as more subtle spasms that might for example affect the head only. Each individual spasm usually lasts clinically for less than a second but they tend to occur in batches ranging from a few, to hundreds of spasms occurring in quick succession. They often take place as the infant is waking or falling asleep and may be associated with a cry. Hypsarrhythmia is the term given to a characteristic highly chaotic, high voltage pattern seen on EEG pathognomonic for this syndrome. There are many underlying etiological factors that may predispose to the development of infantile spasms but in as many as 30% of cases no cause in found. The vast majority of infants diagnosed as having infantile spasms will develop psychomotor retardation. Treatment of the spasms has been notoriously difficult with steroids and benzodiazepines forming the mainstay of treatment over the past fifty years or so. More recently, vigabatrin, one of the new generation of anticonvulsants has been shown to be efficacious in treating spasms in a large proportion of these patients. Refractory epilepsy of other seizure types is common in this group and there is increasing interest in the role of epileptic surgery in those patients shown to have an epileptic focus for the propagation of their spasms.

Partial seizures

Partial seizures are those that arise from a focal area of the brain (as opposed to generalised seizures which involve the whole brain simultaneously). It may be difficult to distinguish between focal seizures that rapidly become secondarily generalised and primary generalised seizures clinically but investigations such as EEG or telemetry (prolonged

video EEG) may help to differentiate between the two. Some partial seizures do not generalise, or do so only slowly. Partial seizures have a range of manifestations; motor, sensory, behavioural or autonomic (previously called psychomotor or temporal lobe epilepsy). In simple partial seizures there is no significant loss of consciousness, whilst in complex partial seizures there is. Some or all types of partial seizures may be present in any one individual.

Typical simple partial motor seizures involve a limb or one half of the face and consist of a clonic movement (a sudden contraction, followed by slow relaxation of the affected muscle). The seizure may be confined to one area or appear to move along the limb – a phenomenon known as a Jacksonian march. Weakness of the affected limb(s) may follow, lasting minutes to hours – a phenomenon known as Todd's paralysis.

Complex partial seizures are often (though not always) associated with a temporal lobe focus. In TSC in particular they are often frontal and can be occipital or parietal in origin (possibly reflecting the position of tubers). The clinical features are wide-ranging and often specific to the individual. They may include olfactory, auditory and even visual hallucinations, which are accompanied by automatisms such as chewing, swallowing, fumbling or doing repetitive movements whilst mumbling in a confused state.

Response to treatment is variable and resistance is not uncommon particularly in complex partial seizures. Surgery should be considered in those shown to have a single epileptigenic focus that continue to have refractory epilepsy.

Primary generalised tonic clonic seizures

These seizures affect the whole brain simultaneously. Clinically, onset is sudden and without warning, with a tonic phase during which the patient become rigid and may appear to stop breathing. This is rapidly followed by the clonic phase; the patient falls to the ground with jerking movements affecting the whole body symmetrically: there may be associated urinary or faecal incontinence and an increase in secretions giving the appearance of foaming at the mouth. This phase can last a variable amount of time and there is loss of consciousness throughout. The patient then regains consciousness but often falls asleep for a period of time: the post-ictal phase. A large choice of drugs is now available for this type of seizure, though many have adverse side effects. It is often a matter of trial and error to discover which treatment best controls the fits without causing unacceptable side effects in any individual patient. Surgery is not usually an option in these

patients. Secondary rapidly generalised partial seizures are probably the usual aetiology of apparent generalised tonic clonic seizures in TSC and are best treated as such.

Myoclonic seizures

These are a type of generalised seizure (i.e. the whole brain is affected simultaneously). They have a sudden onset without warning, tend to be very brief and may affect any muscle group. Sometimes there is loss of consciousness associated with a sudden contraction of the muscles resulting in the patient been thrown to the ground with some considerable force. These are known as "drop attacks" and frequently result in injury, especially to the face and head. Treatment is problematic and it is not uncommon for these fits to be refractory to treatment. Akinetic attacks resemble drop attacks in as much as there is loss of consciousness and the patient drops to the ground, but in these seizures there is sudden and total loss of muscle tone rather than forceful contraction of the muscles.

(Convulsive) status epilepticus

This is usually defined either as convulsions lasting longer than a given time (most often thirty minutes) or successive convulsions such that the patient does not recover consciousness between them. This term encompasses any type of seizure but it most commonly presents as generalised tonic clonic seizures. Treatment of status epilepticus is a medical emergency requiring both resuscitation and support of the patient as well as pharmacological control of the fits.

Non-convulsive status epilepticus (NCSE)

Non-convulsive status epilepticus is a rare but severe type of epileptic seizure (see chapter six) in which there is ongoing seizure activity within the brain (this can be seen on the EEG recording), but it may not be obvious that the patient is having a seizure. For example, there may not be any visible jerking of the limbs and the patient may be partially aware of their surroundings, however on closer examination the patient may have clinical features such as drooling, dilating and/or constricting pupils, sweating and palpable jerks. NCSE most often occurs in patients who already have epilepsy that is difficult to control. It most commonly occurs in patients with other seizure types (past or current) such as infantile spasms or Lennox-Gastaut syndrome or other neurological conditions such as TSC. Long periods of NCSE can interfere with development, education and well-being.

The traditional treatment is the intravenous administration of diazepam, which requires hospital admission.

Generalised 3/sec spike and wave

These are a type of generalised seizure consisting of momentary loss of awareness and responsiveness with a corresponding cessation of ongoing activity. There may be associated clonic movements of the eyelids (at three cycles per second) and more rarely of the face or a change in postural tone with either rolling of the eyes (increased) or slumping of the arms and shoulders (decreased). Automatisms are seen in about 60% of cases. They are often associated with triggering factors such as hyperventilation, tiredness or emotion. Recovery is quick and they are rarely associated with a post ictal phase. Diagnosis is often delayed because the events are put down to 'day dreaming', but once it has been made many respond to sodium valproate or ethosuximide. The vast majority also resolve with time and it is rare for them to continue into adult life (although other types of epilepsy may occur). They are usually due to childhood or juvenile absence epilepsy, both genetic syndromes. Typical absence seizures rarely occur in patients with TSC, as they are genetic in origin and are truly generalised seizures. They do not result from secondary generalisation from a focal epileptic focus whether acquired, e.g. head injury, or inherited or in TSC.

Morbidity and mortality in tuberous sclerosis

Although some patients with TSC are only mildly affected and lead a normal life with typical life expectancy (a few may never even be aware that they are affected) there is an immense amount of morbidity associated with this disease. In addition, for the majority of patients there is reduced life expectancy. The purpose of this thesis is to look at the clinical factors that contribute to the morbidity and mortality seen in TSC and examine means of reducing the impact of these factors on the long-term outcome.

There have been few studies investigating the morbidity and mortality in TSC. The two early studies by Critchley and Earl[11] 1932 and Gunther and Penrose[12] in 1935 concentrated on small populations of institutionalised patients giving biased results. Over the past 15 years population based studies have been performed but they have either been based on small numbers of patients (less than twenty) or have concentrated on issues other than morbidity and mortality. Two studies have been carried out looking at morbidity in a large

geographically defined area with a known population of TSC sufferers: Shepherd et al[26] 1992 who looked at the prevalence of TSC in the West of Scotland and then more specifically at the associated seizures and intellectual disability; Webb et al[19] 1994 who looked at the prevalence of TSC in the Wessex region and the related morbidity, neurological and other. The largest study looking at the causes of death in TSC is that of the Mayo clinic (1991) who studied a series of 355 TSC patients[32].

Both Shepherd[26] and Webb[19 25] found seizures and mental retardation to be the major inextricably linked causes of morbidity affecting up to 80% of the TSC population. There are only a few cases of patients who have learning difficulties without a history of epilepsy reported in the literature. In addition, the age of seizure onset correlates with long-term prognosis for psychomotor development. Children who have not developed epilepsy by the age of five rarely regress and are more than likely to have normal intellectual outcome. None of the patients studied by Shepherd[26] or Webb[19 25] who developed epilepsy over the age of five had psychomotor delay.

Seizure type is also an important prognostic factor for long term psychomotor development, with infantile spasms (IS) most commonly associated with a poor outcome. Webb[19 25] et al found that 94% of infants who developed IS subsequently were shown to have severe learning difficulties. Likewise, Shepherd[26] found that seventeen out of eighteen infants presenting with IS had impaired intellect as compared with thirteen out of thirty presenting with other seizure types. They also found that learning difficulty is more common in those that have poor seizure control. IS also account for over half of the primary seizure type in patients with epilepsy and TSC. Although it is not possible to change the age of onset (peak 4–7 months of age) it might be possible to reduce the long-term psychomotor delay either by improving the treatment of these seizures (both in term of number of patients in whom control is attained and the speed at which this control occurs) or by preventing the onset of the spasms from occurring.

However, some believe that mental retardation and epilepsy are not so closely linked. They believe that it is the number and possibly, more specifically, the location of tubers which give rise to the cognitive defects in patients with TSC not the onset of epilepsy. One study has shown that nine patients with tuberous sclerosis considered to have normal intelligence (Average IQ = 99) were significantly more prone to having specific cognitive difficulties

on detailed neuropsychological testing than controls. Only three of their patients also suffered from epilepsy[33]. Nonetheless, this does not explain the developmental regression seen in those developing seizures although it is probable that in most cases it is the tubers that give rise to the epileptic foci.

Psychomotor regression is rarely seen in patients developing epilepsy after the age of five. This regression usually results from the development of NCSE that continues either unrecognised or untreated for long periods of time leading to prolonged periods of impaired consciousness that can interfere with development, education and well being. The problem is that the attacks are often frequently recurring and require hospital admission for treatment. Not only is there a delay whilst admission to hospital is arranged but the admission itself may result in interruption to education. If the parents could be taught to recognise the episodes of NCSE early and administer treatment at home that aborted these attacks, further regression might be prevented and improved education and well-being would result.

Also associated with TSC and learning difficulties is a high incidence of behavioural problems coupled with poor sleeping patterns. In a study, carried out by Hunt[17] in 1993, 60% of parents reported refusal to go to sleep, early wakening and nocturnal hyperactivity in children with learning difficulties as the hardest problems to cope with. A study performed in Sweden[16] also found that most of the children had behavioural problems such as autistic traits, hyperactivity, poor sleep, aggression and self-harm. The main difficulty is that these children also respond poorly to traditional sedatives (often becoming even more hyperactive) or to behaviour modification techniques. Melatonin, a natural hormone that is available in synthetic form, has been shown to improve sleep in blind children with developmental delay and may therefore be of benefit in children with TSC.

In Shepherd's[32] review of the causes of death in 355 patients with TSC, forty had died from their disease (nine others died from unrelated causes). Renal disease was the commonest cause of death (twelve patients); seven died of renal failure, three of carcinoma and two of haemorrhage from angiomyolipoma. To date no study has been carried out in the United Kingdom (UK) to look at the incidence of end stage renal failure (ESRF) in TSC or its clinical presentation and no paper has reported the underlying pathology in these patients. Ten of Shepherd's patients died as a result of brain tumours, four died of

pulmonary complications (LAM) and two infants died as a result of cardiovascular disease. Of thirteen patients with severe handicap, nine died as a result of status epilepticus, the other four from bronchopneumonia. It is important, when interpreting these results to note that approximately 60% of patients with TSC have renal complications compared to only 1 –3% of patients who are known to have pulmonary complications and as Shepherd concluded in his paper; "the prognosis associated with pulmonary TSC is less favourable than that associated with other organ involvement in TSC; a higher percentage of patients died of TSC with lung disease than with heart, kidney or brain involvement". Despite this, there is very little in the literature about the pulmonary complications of TSC both in terms of its clinical presentation and association and in terms of treatment and long-term prognosis.

The causes of premature mortality also seem to be age related in TSC. Cardiovascular disease, usually arrhythmia or cardiac failure resulting from rhabdomyomas, less commonly WPW syndrome leads to death in the infant or young child. GCAs most commonly occur between the ages of ten and twenty whilst deaths from lung disease rarely occur under the age of forty. Death from renal disease is also rare under the age of ten and is again age related with respect to the underlying pathology; infants with PKD are often affected earliest with renal failure occurring in the first to second decade of life; AMLs causing haemorrhage become more frequent with increasing age and renal carcinomas tend to occur in older patients (though often at a younger age than the general population)[34].

Aims

The aims of this thesis were:

1. To report a longitudinal population study in a defined group of patients looking at the epidemiology and natural history as well as the morbidity and mortality suffered by this population.
2. To investigate the current treatment regimes for the types of epilepsy (infantile spasms and NCSE) known to be linked with the highest risk of associated learning difficulties to try and determine which are most efficacious in treating the fits by;

- reviewing the treatment of infantile spasms with high dose prednisolone,
- reviewing the use of vigabatrin in the treatment of infantile spasms in TSC,
- setting up the United Kingdom Infantile Spasm Study (UKISS) to compare the efficacy of steroids and vigabatrin in treating infantile spasms,

- undertaking a Cochrane review comparing all medical treatments of infantile spasms in terms of seizure control,
- looking at oral treatments of non-convulsive status epilepticus in TSC.

3. To investigate whether any treatment regime is more efficacious at reducing the incidence of
   long-term psychomotor delay in these patients by;
   - setting up UKISS to compare the efficacy of steroids and vigabatrin in terms of long term developmental outcome,
   - undertaking a Cochrane review: comparing all medical treatments of infantile spasms in terms of long-term developmental outcome.
4. To determine if any treatment regime might be used to prevent the onset of seizures and so prevent subsequent psychomotor delay and to develop a possible model for a prophylactic trial.
5. To investigate the effect of exogenous melatonin on sleep disorders in tuberous sclerosis by;
   - reviewing the literature on the use of melatonin in sleep disorders,
   - looking at the use of melatonin in treating the sleep disorder of TSC.
6. To investigate the natural circadian rhythms in patients with sleep disorder in TSC and compare them with the normal population by;
   - examining at the rhythms of melatonin excretion in children with TSC and sleep disorder and to determine the normal excretion pattern of melatonin in children without TSC.
7. Two important causes of premature mortality in patients are respiratory and renal failure;
   - to examine the prevalence and underlying causes of end stage renal failure in adults with TSC.
   - to undertake a review of the literature of LAM in patients both with and without TSC.
   - to investigate further the natural history and treatment of LAM in TSC.

CHAPTER TWO

A Ten Year Review of the Epidemiology, Morbidity and Mortality of the Tuberous Sclerosis Population in the Bath Health District

In 1996 our group published the first large population based study[19] of 3,400,000 people finding 131 known individuals with TSC in the Wessex region, most of whom were examined for the review, unlike previous prevalence studies. It was also the first review to look at both the epidemiology of this condition and the morbidity associated with TSC, other than seizures and learning disability, which had previously been described.

Aim

To report a longitudinal population study in a defined sub-group of the Wessex study to improve information about the epidemiology and the natural history of this condition, in particular the morbidity and mortality suffered by this population.

Patient selection

Index cases were identified as patients ordinarily resident, within the Bath Health District Authority between the 31st August 1986 and 31st August 1996. Gomez's criteria[2], updated by Osborne[3] were used to confirm a diagnosis in those patients given a diagnosis of TSC on 31st August 1986, whilst the newer criteria of two hamartomas in two distinct organs[4] was used for those given a diagnosis of TSC on 31st August 1996 (see chapter one).

Method

Since 1985 patients suffering from TSC in the Bath district have been identified by one of us (JPO) and followed either regularly in clinic, or if they preferred, followed only if they developed symptoms. Those not seen in clinic have been reviewed by checking their notes, writing to their General Practitioners (GPs) as well as involving them in research studies. Initially in 1986 there was a systematic search as previously reported[19]: since then we have relied on the existence of the TSC clinic, which is well known in the district, as a source of referral. The patients' progress is reported up to August 1996. Patient details include findings from at least one detailed history and examination, and where possible results from Woods light examination, direct fundoscopy, cranial CT or MRI scan, renal

ultrasound scan (USS) and echocardiography, supplemented by further investigation as indicated.

Normal intellect was defined using Webb et al's definition used in the original cohort of patients defined in 1996: patients able to talk, read, write and undertake self care e.g. dressing, feeding and toileting were assumed to have normal intellect[19].

Results

Prevalence and incidence

In Webb et al's ascertainment in 1986[19] there were 19 patients with TSC resident in the Bath district. Since that time:

- Three patients have had their diagnosis withdrawn as a result of the new diagnostic criteria. One patient has bilateral renal AML but no other stigmata of TSC. The other two patients belong to a large family with TSC affecting five generations. One had a single ungual fibroma (which has since disappeared) the other was thought to be an obligate carrier, but this is now known not to be the case; the other affected members of this family all have proven gene defects which these two individuals do not have[35].
- Two patients who were present in 1986 have been subsequently ascertained.
- Five patients have been born since 1986 and subsequently diagnosed as suffering from TSC; three had a strong family history (though one was a new mutation); two are sporadic cases.
- One patient has moved into the Bath district.

This brings the total number of known patients in the Bath district on 31st August 1996 to 24, giving a total of 200 patient years of observation and 628 patient years of existence.

		years of prospective observation	years of existence (prospective and retrospective observation)
Known TSC patients in 1986	**19**	190	673
Diagnosis withdrawn	**-3**	-30	-116
Diagnosed post 1986	**2**	8	34
Born into Bath district	**5**	30	30
Moved into the Bath district	**1**	2	7
	24	**200**	**628**

Bath Health District covers a population of ~417,000 people (1996) giving an estimated prevalence of TSC of 1:17,000 (5.3 per 100,000).
In the Bath district there are approximately 5,500 live births per annum giving an estimated birth incidence of 5:55,000 or 1:11000.

Population

The mean age has remained static at around 26 years over the ten-year period, but the age at diagnosis has decreased from 18.8 years to 15.5 years. There were no deaths recorded during the ten-year period.

In 1986 there was a predominance of affected females of 1.7:1 but in 1996 there were equal numbers of affected males and females.

Genetics (table one)

In 1986 ten patients had an affected parent (although nine of these were from one family) and nine were sporadic cases i.e. neither parent affected, this gives a spontaneous mutation rate of 47%. In 1996 nine patients had an affected parent (again eight were from the one family) and fifteen were sporadic cases, giving a spontaneous mutation rate of 63%.

Ideally for a diagnosis of TSC to be excluded in the parents, there should be absence of skin and eye signs and a normal CT Brain. At one time, a renal ultrasound was also performed but this is now thought to be unhelpful (due to regular normal occurrence of renal cyst(s) in adults) and is no longer routinely performed[36]. 46% of parents chose or for other reasons could not be examined and / or screened.

In Bath three patients have had the diagnosis of TSC withdrawn over the past ten years; one had bilateral renal AML and according to Osborne's contemporary criteria[3] fitted the criteria for TSC, but with the modification of these criteria, it is now recognised that bilateral renal AML can occur independently of TSC[37] and with no other stigmata present this patient is no longer considered to have a diagnosis of TSC.

Table one

Patient	Mother				Father			
	Woods light	Fundi	Cranial CT scan	Renal USS	Woods light	Fundi	Cranial CT scan	Renal USS
1	√				√			
2	√	√	√		√	√	√	
3	√	√	√	√	√	√	√	√
4	√	√						
5	Not screened				Died before patient diagnosed			
6	Not screened				Not screened			
7	√	√	√	√	√	√	√	√
8	√	√	√		√	√		
9	Not screened				Not screened			
10	Not screened				Not screened			
11	√	√	√	√	√	√	√	√
12	√	√		√	√	√		√
13	Patient adopted - not in contact with biological parents							
14	Not screened				Not screened			
15	√		√	√	√	√		

CT = computerised tomography, USS = ultrasound scan.

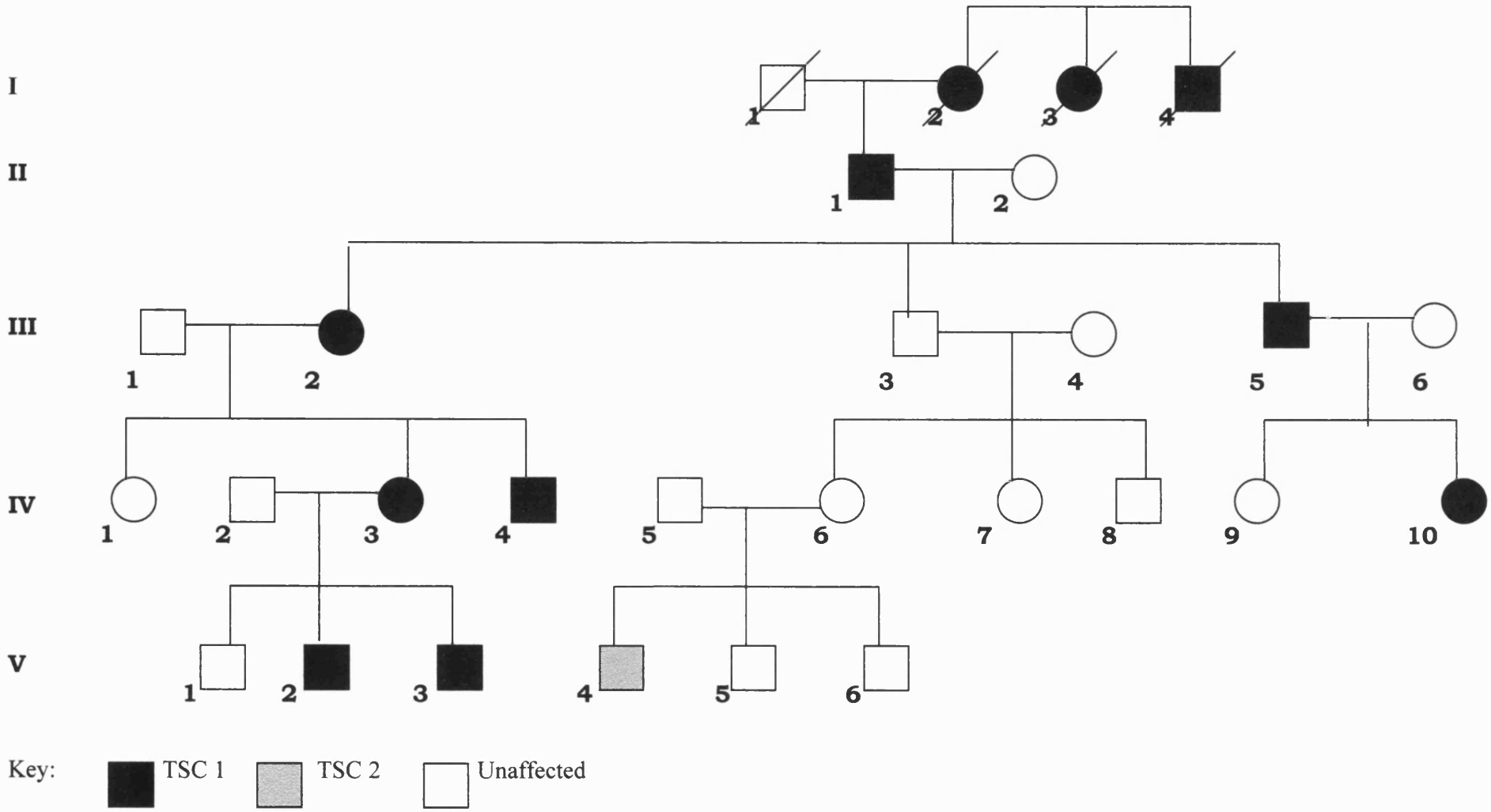
Table showing how TSC was excluded in the parents of sporadic cases. For the diagnosis to be definitely excluded skin and ophthalmological and CT investigations should be performed but some parents declined.

The other two patients belong to a large family that was known to carry the TSC 2 gene in 1988 (pedigree one).

Fryer[38] et al first reported this family in 1987 as "a family where tuberous sclerosis has probably affected five generations, but where none of the members has been mentally retarded and there is no history of seizures". At that time it was thought that TSC was caused by a single gene mutation and in the same year a gene locus was discovered on chromosome 9 (TSC 1)[6]. Since then six children have been born into the family.

In 1987 IV.3's first son (V.1) was found to have echo dense lesions on his echocardiogram. Initially it was thought that these were rhabdomyomas, placing him at high risk of suffering from TSC. He was re-scanned a year later, and in retrospect, with the increased experience and knowledge in this area, the lesions were not thought to be rhabdomyomas. Although he has not undergone cranial imaging, he has no fits, learning difficulties or

Pedigree one



neurocutaneous manifestations of TSC and Woods light examination, renal USS and fundoscopy have all proved negative so far, making the diagnosis unlikely. He has now been shown not to have the mutation in TSC1 which his mother and brother have (JPO personal communication).

In 1988 IV.6 (previously thought to be unaffected) had her first child (V.4). At the age of 13 months V.4 developed epilepsy following his measles, mumps and rubella (MMR) vaccination. He subsequently went on to develop severe learning and behavioural difficulties. On investigation he was found to have subependymal nodules, bilateral renal AML and retinal phakomas in both eyes. He has also developed angiofibroma and hypomelanic patches leading to the unequivocal diagnosis of TSC. IV.6 was extensively investigated: CT and MRI brain, renal USS, echocardiogram and examination of the skin, including Woods light were all negative. It was therefore reported that this family contained an individual (III.3) with minimal expression (under the diagnostic criteria in use at that time III.3 was thought to have TSC as he had a first degree relative and a single ungual fibroma: under the current criteria he would not be considered to suffer from TSC) and an individual with non-penetrance[39]. IV.5 has also subsequently been investigated as IV.6 and found to not be affected. V.4 was therefore the first member of this family now spanning at least six generations to suffer from epilepsy and learning difficulties. However, it had become apparent that a second gene existed and its location on chromosome 16p13 (TSC2) was discovered in 1992 by Kandt[7], and was cloned a year later by Nellist[8]. The TSC1 gene was then cloned in 1997[9]. This family has since undergone DNA testing and all definitely affected members found to carry TSC1 mutation **except** V.4 who has been found to have a TSC2 mutation, IV.6 and her father (III.3) tested negative for both gene defects. We now believe V.4 to be a sporadic mutation occurring within this family carrying the TSC gene. Interestingly, the hypothesis that the clinical phenotype of TSC1 is not as severe as TSC2 is compatible with the information from this family.

IV.6 (in 1989) had another son (V.5) in 1989 who appears, as yet to be unaffected.

In 1990 V.2 was born to IV.3. He was found to have three rhabdomyomas on echocardiogram at two weeks of age, a repeat echocardiogram at seven weeks showed them to have regressed without causing any symptoms, a phenomenon increasingly recognised in this condition. He has also subsequently been shown to have tubers on MRI

imaging and AML on renal USS. He developed seizures and also has mild learning difficulties and behavioural problems, though not as severe as V.4.

In 1993 IV.3 had her third son V.3. He was admitted to the neonatal intensive care unit on the first day of life following a cyanotic episode on feeding. An ECG showed WPW syndrome coupled with SVT; echocardiology showed a rhabdomyoma on the aortic valve causing outflow obstruction. Initially he was successfully treated with diuretics and digoxin, but by two months of age continuing attacks of aortic obstruction required surgical removal of his rhabdomyoma which had not decreased in size. He has since gone onto develop a shagreen patch, confirming the diagnosis of TSC.

The sixth boy to be born into this family is V.6. At the time of IV.6 pregnancy with V.6 it was still believed that she could be an obligate carrier. In the third trimester she experienced some abnormal foetal movements, which she described as repetitive jerking movements. Although fits starting in utero had not been previously described in TSC, with the family history, this was the concern. After lengthy discussion with the parents it was decided to undertake an antenatal MRI scan to try and establish whether or not the baby was likely to be suffering from TSC. It was performed at 36 weeks gestation. The foetus was sedated by giving IV.5, the mother, an oral sedative of 10mg diazepam approximately 20 minutes before the scan. T1 weighted images of the foetal brain were obtained in axial, sagittal and coronal planes. Good quality images were obtained but (now unsurprisingly) no abnormalities were detected. V.6 is now eighteen months old and has no stigmata of TSC.

Referral patterns (table two)

The referral patterns are summarised in table two and are given for all 24 patients who have resided in the Bath district over the past ten years. In the last ten years, seven new patients have been diagnosed. Two were brothers born into a family with a family history of TSC spanning five generations; both had skin stigmata confirming the diagnosis. In addition, the younger son also had a cardiac rhabdomyoma that was diagnosed on the first day of life. Four others presented with epilepsy and were found to have either skin stigmata and/or an abnormal brain scan (one also had a strong family history). The final patient was diagnosed because of his facial angiofibroma.

Table two

	Reason for:			
	Referral	**Diagnosis**	**Other features**	**Total (n=24)**
Affected relative	7 (29%)	-	-	-
Incidental referral	1 (4%)	-	-	-
Epilepsy	12 (50%)	-	16 (67%)	16 (67%)
Abnormal brain scan	-	7 (29%)	4 (17%)	11(46%)
Giant cell astrocytoma	-	-	1 (4%)	1 (4%)
Developmental delay	-	-	10 (42%)	10 (42%)
Behavioural problems	-	-	8 (33%)	8 (33%)
Cardiac disease	-	2 (8%)	2 (8%)	4 (17%)
Renal disease	2 (2%)	2 (8%)	12 (50%)	14 (58%)
Lung disease	-	1 (4%)	-	1 (4%)
Retinal phakoma	-	3 (12.5%)	4 (17%)	7 (29%)
Skin signs	4 (17%)	23 (96%)	1 (4%)	24 (100%)

Table showing the referral patterns for the diagnosis of TSC (N.B. some patients may have had more than one reason for referral).

Skin stigmata (table three)

All 24 patients in Bath have skin signs, but this was not always true at presentation. The most common dermatological features are facial angiofibroma, hypomelanic macules, shagreen patches and ungual fibroma.

Table three

	1986 (n=19)	**1996 (n=24)**
Facial angiofibroma	16 (84%)	22 (92%)
Hypomelanic macules	10 (53%)	15 (63%)
Forehead plaque	7 (37%)	10 (42%)
Shagreen patch	9 (47%)	12 (50%)
Confetti	2 (11%)	3 (13%)
Poliosis	2 (11%)	4 (17%)
Nail fibroma / ridging	12 (63%)	14 (58%)
Gum fibroma	2 (11%)	2 (8%)

Table showing the skin lesions experience by the 24 patients. All 24 patients had skin stigmata of TSC. The two patients who did not have angiofibroma both had a shagreen patch.

Retinal phakoma

Nineteen patients have had their retina examined by fundoscopy, eight (42%) of whom were found to have retinal phakoma. One patient was also found to have amblyopia, which may have arisen as a result of his phakoma overlying the macula and interfering with the development of vision. Another patient is known to have a squint.

Seizures (table four)

In 1986 eight (42%) patients had suffered from epilepsy, by 1996 fourteen patients (58%) had a diagnosis of epilepsy. Equal numbers of males and females are affected.

Type of seizure (table four)

Table four

Patient gender	Age of onset	Type at onset	Other types	LD	Outcome of seizures	Behavioural problems
F	12 Weeks	GTC	CPS, Absence, NCSE, Drop	Y	Refractory	Y
F	4 Months	IS	GTC, CPS	Y	~ 2 / year	Y
F	4 Months	IS	Focal	N	Stopped	N
F	11 Months	GTC	None	Y	Stopped	N
F	5 Years	CPS	GTC	N	Controlled	N
F	5 Years	GTC	None	N	Controlled	N
F	18 Years	CPS	None	N	Stopped	N
M	1 Month	Focal	IS, GTC, Absence, Drop, NCSE	Y	Refractory	Y
M	6 Months	IS	GTC, Absence	Y	Refractory	Y
M	7 Months	IS	Absence	Y	Controlled	Y
M	8 Months	GTC	Focal	N	~2 / year	N
M	9 Months	IS	None	Y	Stopped	Y
M	13 Months	GTC	Absence	Y	Refractory	Y
M	18 Months	Absence	None	Y	Refractory	Y

LD = moderate / severe learning difficulties, IS = infantile spasms, GTC = generalised tonic clonic, CPS = complex partial seizures, NCSE + non-convulsive status epilepticus, Y = Yes, N = No.

Table showing patient gender, age at onset of seizures, the type of seizure at onset, other seizure types experienced, presence or absence of moderate or severe learning difficulties and behavioural problems and the outcome of the seizures.

There were many seizure types recorded with many patients experiencing more than one type. In total five patients had infantile spasms (IS), five had primary generalised tonic clonic seizures (GTC), one had atypical absence, two had complex partial (CPS), and one focal seizures as their first seizure type.

Outcome of seizures (table four)

Five patients had IS as their primary seizure type with onset under one year of age. All these patients developed further seizure types and all but one have severe learning difficulties.

In total eleven patients had onset of seizures before the age of five. Nine have moderate to severe learning difficulties. The three patients in whom the seizures started after the age of five, and the ten patients who have never suffered from fits, all have normal intellect (as defined by Webb).

Seven females have suffered from epilepsy, in five the fits have either stopped or are completely controlled by anticonvulsants, one continues to suffer the occasional fit only and the seventh patient continues to have poorly controlled fits with multiple seizure types. Three have learning difficulties. Seven males have suffered from epilepsy. In one the fits have stopped and in one they are controlled on vigabatrin. One other patient continues to have occasional fits off anticonvulsants. The other four all continue to have poorly controlled epilepsy despite anticonvulsant therapy. Six have learning difficulties.

Two children developed episodes of NCSE. Both have been successfully treated with oral diazepam.

Learning difficulties and behavioural problems (table four)

In 1986, four patients had learning disabilities and three behavioural problems. In 1996 nine had learning disability and eight behavioural problems. All patients with behavioural and/or learning disability suffered from epilepsy.

Other neurology

One patient known to have TSC developed symptoms of raised intracranial pressure and was diagnosed as having a giant cell astrocytoma (GCA), which was successfully removed without sequelae. One other patient has a mild hemiplegia.

Renal disease

Twenty-two patients have undergone at least one renal USS. Thirteen of these patients were shown to have at least one renal lesion. Five patients had cysts; three unilaterally, one bilaterally and one had adult type PKD. Eleven had renal AML, seven of which were bilateral. One patient had a renal carcinoma.

Only three patients experienced symptoms of haematuria and pain; all three were known to have large bilateral AML, and CT scanning confirmed renal haemorrhage arising from an AML in each case. They were all successfully treated by selective renal artery embolisation. The renal carcinoma was detected on a research scan; the patient had been entirely asymptomatic. The diagnosis was confirmed by biopsy and the patient had a left nephrectomy performed.

Cardiac disease

Twelve patients have had an echocardiogram. Three patients under the age of one and one adult patient had evidence of rhabdomyomas. One had hypertrophy probably secondary to his long-standing essential hypertension. The others were all normal. Two of the three infants showed complete resolution of the rhabdomyomas, on repeat echocardiograms.

One patient (who also had a large cardiac rhabdomyoma causing outflow obstruction) was found to have Wolff-Parkinson-White Syndrome.

Lung disease

Only one patient has been diagnosed as suffering from pulmonary lymphangioleiomyomatosis (LAM) in the Bath district in the past ten years. She presented with a pneumothorax at the age of 21 years treated by pleurectomy, which has not recurred, but she continues to have exercise induced dyspnoea and episodes of haemoptysis despite treatment with methyl-progesterone. Her spirometry shows a reduced vital capacity of 35% predicted, an FEV_1 of 38% predicted and a peak flow of 95%

predicted. High Resonance CT (HRCT) scanning showed multiple thin walled cysts and peripheral bullae confirming the diagnosis of LAM.

The chest X-rays of three other patients (performed for other reasons) were reported as normal.

Discussion

Although patients with TSC may have a normal life span, and one patient in Bath is now in his ninth decade and has suffered no serious complications, it is a disease associated with high morbidity and early mortality. As discussed earlier it can affect almost any tissue in the body, although the most troublesome complications arise from involvement of the neurological, renal, cardiovascular and respiratory systems.

The disease also has important genetic implications. It is an autosomal dominant condition, thus, any patient diagnosed with TSC will have a 1 in 2 risk of passing the disease to each of their off spring. Although it may be possible that the TSC1 phenotype is not as severe as the TSC2 phenotype, severity of disease does not run in families (there are many cases of only mildly affected patients having children who are severely affected) and it is impossible to predict who will be most affected. About half of patients with TSC have severe learning difficulties and epilepsy[25] [26]. Therefore, a patient with TSC will have approximately a 1 in 4 chance of having a child with TSC and epilepsy and severe learning difficulties.

It is important, to make the correct diagnosis, not only because of the possible complications that might arise in the affected individual, but also so that accurate genetic counselling may be given. Presently, it is not possible to routinely test DNA from individuals with TSC (research has isolated TSC1 and TSC2 gene defects in approximately half of affected families) but it is possible to detect TSC on chorionic villus sampling or amniocentesis when a parent has a known mutation. Even though prenatal diagnosis will be possible for the majority in the near future it is unlikely that a test will be available that will predict the severity of the disease in an affected foetus. Therefore, the diagnosis is still frequently a clinical one and the diagnostic criteria need to be modified accordingly as our knowledge of the disease improves to allow both accurate diagnoses and exclusion to be made.

Over the past ten years the age of diagnosis has gradually decreased. This may be explained in part by the fact that three patients had a known family history, so that the family and health professionals were aware of their risk of inheriting the disease. It is also possible that greater awareness of this disease and improving technology have contributed to earlier diagnosis. However, these figures must be treated with caution, as the number of patients is small.

The most common causes of morbidity in the Bath TSC population over the last ten years were seizures and learning difficulties coupled with behavioural problems. Both Shepherd[26] and Webb[19] also found seizures and mental retardation to be the major causes of morbidity affecting up to 80% of the TSC population. There also appears to be a close relationship between seizures and severe learning difficulties. There are only a few cases of patients who have learning difficulties without a history of epilepsy reported in the literature and in those that do it may be some other mechanism other than the TSC that accounts for their impaired intellect. None of our patients who were seizure free had learning difficulties. In addition the age of seizure onset correlates with long-term prognosis for psychomotor development. Children who have not developed epilepsy by the age of five rarely regress and are more than likely to have normal intellectual outcome. None of our patients who developed epilepsy over the age of five had psychomotor delay.

Seizure type at onset is also an important prognostic factor for long term psychomotor development with infantile spasms (IS) associated with the highest risk of severe learning difficulties (SLD). In our group the most common seizure type at onset was IS, followed by generalised tonic clonic (GTC) and then partial seizures. Four out of five patients with IS had SLD, and interestingly the one patient who had normal intellect was the only patient in whom the spasms were rapidly controlled (although the electroencephalogram (EEG) did not show hypsarrhythmia bringing the diagnosis into doubt, it was obtained after treatment had been initiated which might have lead to resolution of the hypsarrhythmia). Because of the long-term psychomotor implications of early onset epilepsy in this group of patients, it is of paramount importance that fits are recognised quickly, accurately diagnosed and treated promptly. Though no study has been undertaken to show that early intervention will improve outcome in these children, many clinicians believe that the quicker the fits (particularly when they are IS) are controlled the better the long-term

prognosis for development. Any infant who is known to suffer from TSC or is at high risk (i.e. has a first-degree relative) must be closely monitored for the development of fits especially IS. If any concerns arise they should be admitted to hospital the same day for observation and EEG monitoring. If the diagnosis is confirmed, treatment should be started immediately. The treatment of IS in the past has been notoriously difficult, but early studies have suggested vigabatrin to be particularly efficacious in treating patients with TSC, controlling the spasms in over 90% of patients[40]. Vigabatrin is also effective in treating partial seizures (the second commonest type of seizure at onset) in these infants[41].

Gender may also be an important prognostic factor for outcome of seizures. Although our numbers are very small and the observation will have to be repeated on larger populations, girls might have a more favourable outcome than boys. Equal numbers of males and females suffered epilepsy but only one girl continues to have refractory epilepsy as compared with four boys. Likewise only three females have moderate to severe learning difficulties compared to six males.

Behavioural problems commonly occur in children with learning difficulties and/or epilepsy. They often exhibit autistic traits and are commonly hyperactive with poor sleeping patterns. In a survey carried out in 1994[27] parents complained that one of the most difficult aspects to looking after their children with TSC was the hyperactivity and poor sleeping. It is also known that these children respond badly to traditional sedatives (often becoming more hyperactive) and behavioural therapies are often ineffective.

Giant cell astrocytomas are another recognised neurological complication of TSC and occur more commonly than in the general population. There is controversy as to whether they arise from subependymal nodules or occur de novo. They most commonly occur around the Foramen of Munro, frequently occurring around adolescence and are rare over the age of thirty years. They usually present with raised intracranial pressure: headache, vomiting, ataxia, drowsiness, diplopia and papilloedema. Treatment is surgical removal. Unlike other forms of brain tumours, the prognosis is excellent. The Bath patient was not typical of patients with TSC who develop astrocytomas, as she was 37 years old. She had long-standing epilepsy, though was taking no treatment. She complained of increasingly severe intermittent headaches, episodes of loss of consciousness and weakness of her legs on head movement. A CT brain scan confirmed a GCA obstructing the Foramen of Munro

causing obstructive hydrocephalus. The operation and post-operative period were uneventful and she was discharged home on anticonvulsant medication. She remains well and symptom free seven years later. This case illustrates the need for vigilance when reviewing patients with neurological symptoms and a diagnosis of TSC.

The only other neurological complication recorded in this group was a hemiplegia. This patient was diagnosed as having IS at the age of four months. Treatment with prednisolone was commenced with resolution of the spasms, but then she developed right-sided fits that continued until the patient was three years old when they resolved spontaneously. Over the ensuing years it became apparent that she had a mild right-sided hemiplegia although in all other aspects she had made excellent progress and had normal intellect. We can only speculate as to whether the hemiplegia is secondary to the right-sided fits or is another neurological manifestation of the TSC, possibly due to the location of a tuber.

Two thirds of the Bath population are known to have renal lesions, but the majority remain asymptomatic. The patients in our survey represented the wide spectrum of renal disease seen in TSC, most commonly AML and/or cysts with, more rarely PKD and adenocarcinoma. As discussed above the TSC2 gene is close to the PKD1 gene. Although PKD1 mutations do not underlie the cytogenesis in all patients (cysts can occur in TSC1 and TSC2), early onset bilateral PKD occurs with a contiguous deletion of both TSC2 and PKD1. Only one patient in our survey has PKD – she is known to be mosaic for a deletion on chromosome 16 affecting both genes. AMLs also occur in both TSC1 and TSC2. The severity of renal disease between the individuals also varies widely. Many patients with AML with or without cysts have remained asymptomatic with normal renal function throughout their life, whilst others have suffered from haematuria, anaemia, pain and haemorrhage (which can be life threatening)[34].

Over the past ten years four of our patients (13%) have undergone treatment for renal complications. Three suffered haemorrhage from large AMLs requiring embolisation and one was found to have a renal carcinoma which was removed surgically. Selective arterial embolisation should now be now the treatment of choice for patients suffering from haemorrhage from renal lesions. In the past nephrectomy was frequently performed but, as in our patients, both kidneys are often involved. When bleeding then occurs in the remaining kidney, this may result in a second nephrectomy (either because of catastrophic

haemorrhage or if embolisation is not successful) leaving the patient reliant on dialysis unless they are fortunate enough to receive a successful kidney transplant. Although none of our patients suffer from ESRF, it does contribute a significant degree of morbidity and mortality within the TSC population as a whole[42]. DMSA scanning and creatinine excretion following selective embolisation does show the remaining part of the treated kidney to be contributing significantly to renal excretion and therefore function. Nephrectomy still remains the treatment of choice for renal carcinoma.

Cardiovascular complications can also occur in TSC and may be life threatening. Cardiac rhabdomyomas are the commonest cardiac manifestation. Three patients in our survey were found to have rhabdomyomas in early infancy, in two of which the lesions were shown to regress and eventually disappear on echocardiology. The other patient was noted to have a large rhabdomyoma in adult life. It is generally accepted that, unlike other hamartomas in TSC which tend to become more numerous and larger with increasing age, rhabdomyomas generally regress, becoming smaller and less common with age. However, the size and position of the rhabdomyoma in this older patient makes it unlikely that it was present in infancy, as she had experienced no symptoms. This raises the possibility that some rhabdomyomas may increase in size after birth; whether arising de novo or from a smaller congenital rhabdomyoma is not known. One possible explanation for the changing size of rhabdomyomas is that they are under the influence of oestrogens. It has been postulated that other manifestations of TSC such as AMLs and LAM are affected by oestrogens (see chapter seven) and it is possible that rhabdomyomas are similarly affected. It could be hypothesised that as oestrogen levels increase during pregnancy, growth of the rhabdomyomas is stimulated so that they reach their maximum size at birth. After parturition, as oestrogen levels fall, the growth of the rhabdomyomas is no longer stimulated and their size regresses, so that they can no longer be detected on echocardiology. Likewise if in later life a patient is exposed to high levels of oestrogens (e.g. ovarian tumour) then a rhabdomyoma may either increase in size once again, or even develop de novo. It is not known whether or not our patient was exposed to high levels of oestrogens.

The majority of rhabdomyomas remain asymptomatic but they can cause heart failure if they arise in a position that causes obstruction to the flow of blood within the heart, or as in one of our patients, syncope due to acute but intermittent obstruction. A less common

problem is the development of WPW syndrome and associated SVTs. It nearly always occurs in conjunction with rhabdomyomas and usually presents within the first year of life, with approximately half presenting on the first day of life. It responds well to medical treatment and will often resolve in later life[43].

Only one patient had been symptomatic and therefore diagnosed as having LAM. She presented at the age of 21 years with sudden onset of chest pain and shortness of breath as a result of a pneumothorax. Pulmonary involvement in TSC is undoubtedly rare. It is difficult to estimate the true incidence, partly because the few studies that have attempted to do so have generally used small numbers of patients from biased groups and partly because it is unknown how many patients with pulmonary complications become symptomatic and therefore recognised. We now know of at least one other patient who may have had asymptomatic LAM during this 10 year period, but only came to light later when she became symptomatic. At present we have no proven method of screening our TSC population for asymptomatic LAM. Previous studies have estimated 1 – 3 % of patients to be affected[44]. It predominately affects females of child bearing age although rare cases occurring in men and children have been reported[45] [46]. The commonest presenting symptoms are dyspnoea and pneumothorax, as in our patient. Other symptoms include chronic dry cough, haemoptysis, wheeze, and chest pain. Development of cyanosis, respiratory failure and cor-pulmonale can also occur[44]. Our patient is currently receiving monthly injections of methyl progesterone and, though she remains symptomatic she has not suffered any further pneumothoracies and has had a moderate improvement on pulmonary function testing. This complication is reviewed in detail in chapter seven.

Skin lesions are nearly universally present in patients with TSC. All the patients in the Bath district had skin lesions that are pathognomonic for TSC. All but two have facial angiofibroma and they both have a shagreen patch. One of these patients is seven, the other four years and it is well recognised that angiofibromas most commonly develop after the age of five and may even arise in adult life. On the other hand hypomelanic patches (best visualised by a Woods ultraviolet light) are often, though not always, present at birth. They can arise later. One patient was examined at the age of 13 months with a Woods lamp; four hypopigmented lesions were noted and documented. Two years later he was re-examined with the Woods light and was found to have twelve new hypopigmented lesions (sixteen lesions in all). The neurocutaneous lesions do not contribute to the potentially lethal

morbidity of this condition, but many of the lesions are unsightly and are of great cosmetic concern to the patient. Treatment for the facial angiofibroma has progressed dramatically over the past ten years due to the introduction of laser treatment. Though blistering of the superficial layers of the skin does occur immediately after the laser treatment permanent scarring is rare. It was also thought that if the treatment was carried out at a young age the lesions would recur, but this does not appear to be the case so that the major limiting factor for age at which treatment can be undertaken is the ability to lie still. A general anaesthetic can be used, but several treatment sessions are required.

No deaths occurred in our population: this might be accounted by both the small numbers and the relatively young age of the population.

Conclusion

Although there were no deaths in the Bath TSC population over the past ten years there is a high rate of morbidity with seizures, associated learning difficulties and behavioural problems affecting two thirds of the population. Symptomatic renal disease affected over 10% of our population necessitating either selective embolisation or nephrectomy. Although renal failure requiring renal replacement therapy had not yet intervened in any of our patients it remains an important cause of premature mortality in TSC. Lung complications (LAM) do appear to be rare within the TSC population, becoming symptomatic in only a small minority of patients. Nonetheless, it is not known how many patients have asymptomatic lung involvement and whether screening patients might be beneficial. Theoretically, at least, anaesthesia and flying may precipitate pneumothoracies, respiratory failure and even death in some affected (but previously asymptomatic) patients. There is very little information available about the effectiveness of treatment and long-term outcome in this group of patients. Other complications contributing to morbidity within our group of patients included cardiac manifestations, GCA and hemiplegia and amblyopia.

This study has also shown that it is possible to undertake long-term studies that give us improved understanding of the natural history of a disease. However, despite the large number of patient years observed (628), a larger study is required to examine lower risk complications such as LAM in more detail. Nonetheless, this study helps confirm that epilepsy, learning difficulties and behavioural problems are the most frequent problems encountered in TSC and occur in as many as two thirds of patients. This type of study also allows observation of time patterns of the complications: for example, although the skin

manifestations of TSC are almost universal, most patients do not develop angiofibroma until after the age of five and the number of hypomelanic patches may also increase with age. Another way to present this data so that the effect of age, time and cohort can be simply visualised would be the use of a modified Lexus diagram.

CHAPTER THREE

Epilepsy and Learning Difficulties

As discussed previously and shown in chapter two, seizures and the associated learning difficulties are two of the most important causes of morbidity in TSC affecting over half of the population. About two thirds of affected patients will develop their epilepsy within the first year of life. The most common seizure type at onset is infantile spasms (IS) accounting for about 40% of cases, followed by partial seizures and then secondarily generalised seizures. Nearly all patients who experience IS will go on to have learning difficulties, as will many of those suffering from partial seizures. Age at seizure onset as well as type at onset and possibly gender are other important prognostic factors for long-term developmental outcome. It is also believed, though scientific evidence is lacking, that early, good control of the seizures may also improve long term outcome.

Infantile spasms: recognition, treatment and prognosis

159 years ago Dr West wrote a letter to the Lancet describing "a peculiar type of convulsion" occurring in his four month old son, so documenting the first case of IS or what has become known as West's Syndrome. IS are a clinical seizure type which include a peculiar type of seizure and psychomotor retardation, usually with a characteristic electroencephalogram (EEG) pattern known as hypsarrhythmia. There are numerous causes of IS which do not share a known common underlying pathophysiological process, although TSC accounts for 10-20% of cases. There are too many other causes to list them all exhaustively but as a general rule any process that affects brain development or metabolism can cause IS.

Examples of other underlying aetiological factors for infantile spasms include:

- Abnormal brain development e.g.: Neurofibromatosis, Sturge Weber Syndrome, neuronal migration disorders, agenesis corpus callusom, hemi-megalenencephaly.
- Chromosomal disorders e.g.: Down Syndrome (~10%), Cri du Chat (trisomy 13).
- Congenital infections e.g.: maternal rubella, CMV infection.
- Infection e.g.: meningitis.
- Hypoxic –Ischemic encephalopathy whether incurred at birth, antenatally, postnatally or due to pre-term birth.
- Metabolic e.g.: phenylketonuria, organic acidurias, pyridoxine dependency.
- Degenerative brain disease, leukodystrophies (rare).
- Trauma

Despite the huge advances that have been made in medicine IS still remain a poorly understood entity. Although with newer imaging techniques we are more often able to elicit the underlying causes of these spasms, still little is known about their pathophysiological basis and treatment remains problematic.

Epidemiology

IS (from all causes) have an estimated incidence of 0.16 – 0.42[47 48 49 50] per 1000 live births. Little is known about the geographical distribution, but two studies from the USA[47 48], one from Denmark[49] and one from Finland[50] showed incidence rates of 0.16, 0.25, 0.25-0.33 and 0.42 per 1000 live births respectively. Studies have reported either equal sex incidence or a slight preponderance of males ranging from 1:1[49] to 1:4[50] (only one has found an excess of females[51]). Age of onset of the spasms has been reported to occur between 1 day and 6 years of age[52], however the vast majority begin within the first year of life, after which alternative diagnoses including infantile myoclonic epilepsy, are more likely. There is a peak age of onset between four and seven months. One of the main difficulties in estimating the age of onset is the time taken to make the diagnosis. There is often a significant delay between the start of the spasms and their eventual diagnosis: parents may not recognise that there is something amiss; often if they do seek professional advice the spasms are mistaken for colic or a natural startle reflex. In a review by Bobele and Bodensteiner[53] the average lead-time to diagnosis was 3.5 months, but it is well known that this can vary greatly and it is possible that some cases are never recognised.

Genetics

It is rare to have more than one affected member in any family, unless there is another inherited underlying cause for the spasms such as TSC, except in a small number of families where it has been described as having X-linked inheritance[54]. It is more likely that the spasms are a symptom of underlying disease (just as haematuria is a symptom of disease, but can also be idiopathic).

Classification

IS can be classified into three groups;

Symptomatic group: the underlying cause is known prior to the onset of the spasms, for example an infant diagnosed as having Down syndrome or TSC who then subsequently develops IS.

Cryptogenic group: the underlying cause is only discovered following the onset of the spasms for example, a normally developing infant who after the onset of IS, is investigated and then found to have TSC.
Idiopathic group: no underlying cause is found despite investigation.

Unfortunately this classification has led to confusion, as it does not depend on the underlying cause. For example one child with TSC may fall into the symptomatic group, whilst another falls into the cryptogenic group. In addition, with better imaging techniques and diagnostic tools, patients who would have previously been in the idiopathic group, now fall into either the cryptogenic or symptomatic group. Some authors also cause confusion by calling all infants in whom a cause is eventually found as symptomatic and the rest either cryptogenic (assuming there must be a cause) or more correctly idiopathic.

The spasms

No good term has yet been given to this phenomenon that is brief yet fully descriptive. In 1841 West described the sudden forward jerking movement of his son as a Salaam spasm; lightning major convulsions[55], Blitz – Kramp and Jack Knife convulsions[56] have also been used. The problem with these terms is that they only describe the flexor type of spasm. Other terms have been misleading for example, propulsive petit mal[57] suggesting similarity to benign petit mal epilepsy or Pallidum epilepsia[58] falsely implying that the source of the spasm is known. Names that fully describe the spasms such as that used by Gastaut in 1959[59] " Encephalopathic myoclonique infantile avec hypsarrhythmie" are long and cumbersome and are unlikely to be used in English speaking countries. Gibbs and Gibbs[60] coined the phase "infantile spasms" in 1952. Although this is still the best and most commonly used term it is not strictly accurate: not all cases start in "infancy" and a spasm implies to some an abnormal muscle contraction rather than epileptic activity. It has however fallen into general use over many years.

Infancy: this can be defined as "in the first year of life" as infancy is now usually alluded to e.g. infant mortality is death before one year of age, although infant is less precisely defined in the Oxford dictionary as a "child during earliest period of life" thus giving rise to terms such as "infant school"

The commonest type of spasm is the flexor spasm, consisting of sudden generally bilateral and symmetrical contractions of the neck, trunk and extremities. The extent and degree of muscle involvement varies between individuals so that in some, the whole body bends at the waist, the arms are flung upwards and outwards and then brought down, hence the

terms salaam and jack knife, whilst others have only involvement of the neck resulting in head bobbing[61]. Extensor spasms have a predominance of extensor muscle contraction producing an abrupt extension of the neck and trunk with extensor abduction or adduction of the arms and legs[62]. Many infants will have a combination of flexor and extensor spasms during the course of their epilepsy. Kellaway et al 1979[62] found that approximately 34% of infants have flexor spasms, 23% extensor spasms and 42% mixed flexor-extensor spasms Although the vast majority of infants have symmetrical spasms a small minority ~1% have asymmetrical spasms often adopting a tonic neck reflex position.

Each spasm is only visible for a brief duration lasting a few seconds, though persisting EEG changes for a single spasm may last as long as 106 seconds[62]. They tend to run in a series or in batches or clusters ranging from just a few to as many as one hundred, with many studies quoting averages of between 30 and 50 spasms in each batch. The spasms may also be triggered by certain stimuli, the most common being waking or falling asleep[63] though feeding[64] has also been implicated. Some earlier studies suggested that external stimuli such as noise and touch can provoke the spasms but this has only been reported rarely since.

An association of a cry with the attacks is common and has been frequently reported, usually during or after the attack, more rarely before. It may be this cry that leads to the misdiagnosis of colic or intussusception, or the observer to believe the child is in pain[64]. A few authors have reported other phenomena such as tears, hiccups, a laugh or a giggle[63].

It is difficult to evaluate whether consciousness is lost or maintained during these events because of the age of the patients, the brevity of the fit and the frequently associated learning difficulties.

Electroencephalogram (EEG)

Hypsarrhythmia is the most important EEG pattern associated with IS (figure seventeen). It is important to note that this EEG appearance is not present at all times and tends to be modified by both the natural course of the disease and treatment therapy[60]. Synchrony between the hemispheres and between spike and wave components often appear in the later stages of the disease, a pattern termed modified hypsarrhythmia. Hypsarrhythmia is most

commonly seen as the child falls asleep and wakes, but interestingly the EEG often returns to normal during rapid eye movement (REM) sleep[65].

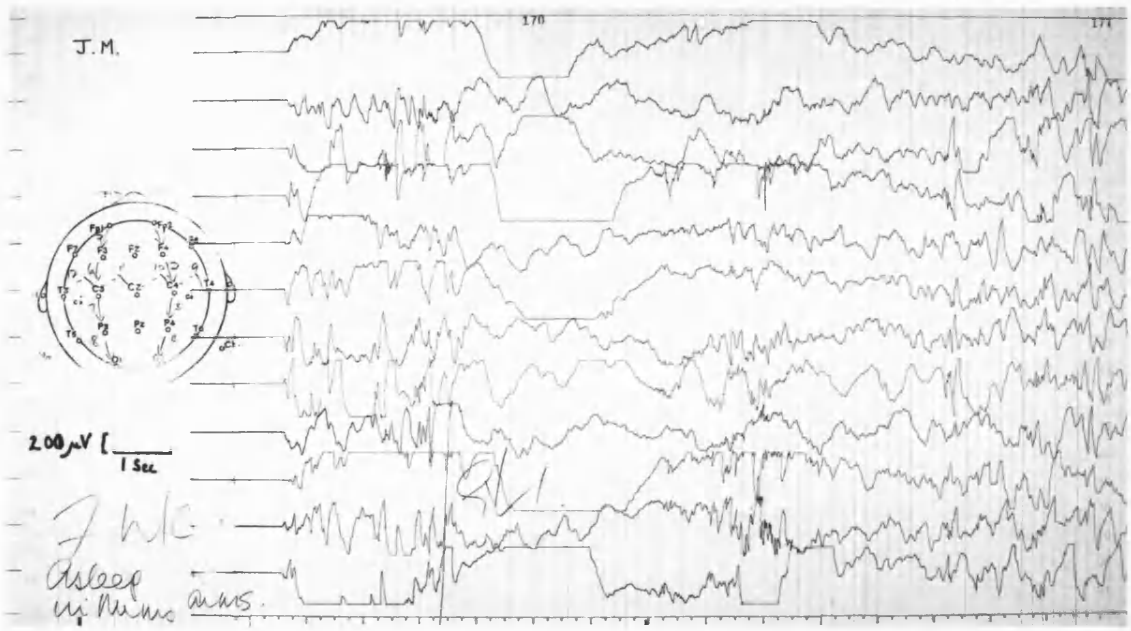


Figure seventeen – EEG showing hypsarrhythmia

Definition of hypsarrhythmia; Gibbs and Gibbs 1952[60] "Very high voltage, random, slow waves and spikes in all cortical areas. The spikes vary from moment to moment in duration and location; at times they seem to come from another focus, or possibly from multiple foci. Occasionally the spike discharge is generalised but it is never rhythmically repetitive or highly organised as in petit mal or petit mal variant. The chaotic appearance of this abnormality gives the impression of a nearly total disorganisation of cortical voltage regulation".

The presence of a focal abnormality within the hypsarrhythmia is not uncommon, and when persistent may suggest a focal lesion within the brain. In patients with TSC such a focus may be the result of an underlying tuber. With the pioneering advances in epilepsy, it may be that in the future this group of patients will be potential candidates for epilepsy surgery.

Developmental delay

The most devastating association of IS is with psychomotor development. Studies in the past have estimated the risk of mental retardation of 80% - 90%[66 67 68 69]. Admittedly, many of the affected infants already have an underlying disorder, which predisposes them to having psychomotor delay, for example Down syndrome or cerebral palsy. Nonetheless, even the children with these types of problems will stop developing as quickly and even regress after the onset of the spasms. Infants with TSC usually follow a pattern of

development within the normal range until such a time that they develop IS after which they show signs of arrested development or regression.

Although it is impossible to predict which children will be most severely affected, good prognostic factors include:

- idiopathic aetiology[66 67 68]
- later age of onset[68]
- single spasms (rather than batches)[63]
- no other fits[67 68]
- absence of focal abnormalities on EEG[66]
- short lag time between onset of spasms and treatment[66 67 68]
- a good response to treatment[67 68]

It is not known whether any particular therapeutic agent is superior to the others with regard to long-term outcome (seizure control or psychomotor development).

There is a definite pattern to the developmental delay. Social skills, such as smiling are lost first. The infant then becomes lethargic, floppy and apathetic and no longer seems aware of or interested in their surroundings: this sometimes leads to concerns about vision and hearing. Motor skills such as grasping and reaching are usually the last to be affected, but gross motor skills can be affected and a few children never learn to walk[65].

In a minority of cases, development is not arrested or may return to normal after the cessation of spasms.

Diagnosis and investigations

Diagnosis is by clinical observation and EEG. Clinical observation is not always easy and can be missed by parents and less experienced nursing and medical staff. It is simple enough when an infant presents with the typical salaam spasms occurring in long batches many times a day, but in the infant with infrequent or single spasms they can readily be mistaken for colic or a startle reflex. The younger the infant, the more difficult it is to detect abnormal movement or delayed development.

It is important that whenever IS are suspected the child is admitted for close clinical observation by experienced staff. An EEG should then be undertaken and if

hypsarrhythmia is not seen, a sleep EEG performed, since hypsarrhythmia may only be present as the infant is falling asleep or waking. Where there is any doubt video and polygraphic recordings may help. Occasionally, it may not be possible to confirm the diagnosis with an abnormal EEG, however, if IS are clinically certain, treatment should be considered because of the poor prognosis of this condition. Some of these infants, with a normal interictal EEG will have a relapse later with severe psychomotor retardation but their management at presentation is controversial, because benign infantile myoclonus does not require treatment and is clinically similar, but without the risk of associated psychomotor retardation: their EEG is normal. In all infants in whom there is no other known cause for their spasms a diagnosis of TSC should be excluded. Brain imaging (CT and/or MRI), examination of the skin with Woods light (for hypomelanic patches) and fundoscopy (for retinal phakomas) should be undertaken as a minimum. Renal USS and echocardiography should also be considered.

Treatment

At least 30 drugs have been tried since Dr West wrote his letter in 1841. Most anticonvulsants have been tried, many with no effect and no treatment has been shown to be successful in treating the spasms in more than about half of the patients, except steroids, valproate and vigabatrin.

The first recorded treatment, after West, was by Gibbs et al in 1954[69], who reported favourable results using chlortetracycline, 113 years after West's letter. It is unclear from the literature whether this delay was due to the fact that IS were not being readily recognised and therefore treated, or whether in fact no treatment had previously been found to have any effect.

Steroids and hormonal treatments have been used in the treatment of seizure disorders since the early 1950's. In 1958 Sorel and Dusaucy Bauloye[70] reported a dramatic response to ACTH therapy in children suffering from IS. Not only did the spasms stop and the EEG improve, often becoming normal, but they claimed that mental improvement occurred if treatment was started within a few weeks of the onset of the spasms.

Following this first report there have been many studies which have frequently confirmed the effect of steroid/hormonal therapy claiming to stop seizures in just over half of the

patients supporting the suggestion that steroid/hormonal therapy is effective in a significant proportion of children with IS. A literature review of the English Language using Medline between 1950 and 1995 found eleven studies and a further review of three studies (fourteen in total) investigating the effect of ACTH and steroids on IS. There were three randomised RCT trials[71 72 73], eight open prospective trials [74 75 76 77 78 79 80] and three retrospective trials [81 82] (see table five). Out of a total of 784 patients treated there was complete cessation of spasms in 449 (i.e. 57%).

Table five

Study	Study design	Selection Criteria	Total No of pts	Drugs	Dose	Admin	Duration	No of patients	siezures stopped	siezures reduced	hyps. resloves	relapses	Cross over	No of patients	seizures stopped
Baram 1996 (71)	RCT	Clinical spasms Hypsarrythmia No prior steroid treatment	29	ACTH Prednisone	150U/m2/day 2mg/kg/day	IM Orally	2 weeks (tap) 2 weeks (tap)	15 14	14 4	N/A N/A	13 4	N/A N/A	Prednisone ACTH	2 8	1 8
Hrachovy 1994 (72)	RCT	Clinical spasms Hypsarrythmia No prior steroid treatment	59	ACTH high dose	150U/m2/day for three weeks	IM	3 weeks (tap)	26	13	N/A	13	N/A	N/A	N/A	N/A
				ACTH low dose	20 - 30 U/day for two weeks	IM	2 weeks (tap)	24	14	N/A	14	N/A	N/A	N/A	N/A
Hrachovy 1983 (73)	RCT	Clinical spasms Hypsarrythmia No prior steroid therapy	24	ACTH Prednisone	20U/day 2mg/kg/day	IM Orally	2 - 4 weeks (tap) 2 - 4 weeks (tap)	12 12	5 4	N/A N/A	5 4	N/A N/A	Prednisone ACTH	7 8	3 4
Glaze 1988 (74)	Prospective	Clinical spasms Hypsarrythmia No prior steroid treatment	64	ACTH Prednisone	20 - 30U/ day 2mg/kg/day	IM Orally	2 - 4 weeks 2 - 6 weeks	64 in total	38 in total						
Hrachovy 1979 (75)	Prospective	Clinical spasms Polygraphic-video No prior steroid therapy	12	Prednisone	2mg/kg/day	Orally	4 - 6 weeks (tap)	12	2	1	2	0	N/A	N/A	N/A
Hrachovy 1980 (76)	Prospective	Clinical spasms Modified hypsarrythmia No prior steroid therpay	5	ACTH	20U/day	IM	6 weeks (tap)	5	5	0	5	2	N/A	N/A	N/A
Kusse 1993 (77)	Prospective	Clinical spasms Hypsarrythmia Pychomotor delay	18	ACTH	0.8mg	IM	4 weeks (tap)	18	6	5	6	N/A	N/A	N/A	N/A
Snead 1996 (78)	Prospective	Clinical spasms (modified) hypsarrythmia	15	ACTH	150U/m2/day	IM	1 week (tap)	15	14	0	14	5	N/A	N/A	N/A
Matsumoto 1987 (79)	Prospective	Clinical spasms	33	TRH ACTH	0.5-1.0mg/day 0.125-0.75mg	iv IM	1-4 weeks 1-4 weeks	13 20	7 15	N/A N/A	3 12	N/A N/A	N/A N/A	N/A N/A	N/A N/A
Schlumberger 1994 (80)	Prospective	Clinical spasms hypsarrythmia No prior steroid therapy No serious malformations No known TSC	94	Valproate HC	40/mg/kg/day 15/mg/kg/day	Orally N/A	2 weeks 2 weeks	94 94	70	N/A	N/A	6	ACTH	15 (9 excluded)	9
Haines 1994 (81)	Retrospective	Clinical spasms Hypsarrythmia	191	ACTH	2-4U/kd/day	IM	1 week (tap)	191	113	N/A	80	N/A	N/A	N/A	N/A
	Retrospective	Clinical spasms Hypsarrythmia	25	ACTH	N/A	N/A	N/A	25	22	N/A	21	N/A	N/A	N/A	N/A
	Prospective	Clinical spasms Hypsarrythmia	52	ACTH Prednisone	150U/m2/day 3mg/kg/day	IM Orally	1 week (tap) 4 weeks (tap)	30 22	30 13	N/A N/A	24 11	N/A N/A	N/A N/A	N/A N/A	N/A N/A
Singer 1980 (82)	Retrospective	Clinical spasms	55	ACTH	40U/day	IM	1 week (tap)	55	42	N/A	42	16	N/A	N/A	N/A

Table showing the results of the literature search for the treatment of infantile spasms with steroids.

The mechanism of action of hormonal therapy in infantile spasms remains poorly understood. Baram et al[71] has proposed that "stress" increases adreno-corticotrophin releasing hormone (CRH) activity causing infantile spasms during a time when brain maturation is occurring, explaining why infantile spasms are age specific. They argue that ACTH acts by suppressing ARH synthesis. ACTH may also act directly by membrane stabilisation, improving the integrity of the blood-brain-barrier and stimulating myelin formation. Steroids such as hydrocortisone and prednisolone have metabolic, anti-inflammatory and immunosuppressive effects that may play a role in spasm suppression but also act directly by inhibiting anterior pituitary and hypothalamic secretion, including ARH.

The problem with steroids are the side effects: potentially life threatening problems include depression of the immune system (leading to overwhelming sepsis) and electrolyte imbalances. There have been few studies investigating the side effects of steroids when used for the treatment of IS. One such study[83], investigating the risk of infection with ACTH therapy in 27 infants, identified 75 febrile episodes, four of which had confirmed bacteraemia and three deaths occurred. However IS occur at an age when febrile episodes are common. The deaths occurred in children who had received large doses (over 100 units ACTH given 2 times a week over three weeks). Less serious side effects, for example hypertension, are often transient but nevertheless cause a certain amount of morbidity. It is difficult to estimate the frequency of these side effects as the study by Riikonen and Donner[83] shows. In their study only 17 out of 64 had their blood pressure routinely measured. Minor side effects, estimated to occur in two thirds of patients, include behavioural changes especially irritability, changes in appetite, weight gain and alteration in sleep patterns. In addition some forms of steroids e.g. ACTH and synacthen involve daily or alternate daily intramuscular injections.

In view of the devastating effect that IS can have on the patient, it is not surprising that most anticonvulsants have been tried for their treatment at one time or another. **Sodium Valproate**, used over the past 15 – 20 years[84 85], has been one of the most successful. Sodium valproate inhibits the breakdown of GABA, a neurotransmitter, thus increasing its availability. It is also thought to have membrane stabilising properties. Siemes et al[86] conducted a trial of valproate therapy in 22 infants with IS. The dose ranged from 45mg to 100mg/kg i.e. much higher doses than those generally recommended in children for the

treatment of epilepsy (30-40mg/kg). Abolition of seizures was obtained in 65% of children within three months of commencing therapy. There are potential problems with valproate therapy and side effects are common. Hepatotoxicity and pancreatitis, although rare, can occur and be life threatening. It may be that the higher than normal doses required and fears of these serious complications, but particularly the length of time to obtain a response (usually weeks or months rather than days), have limited the use of valproate in this disorder.

Vigabatrin, one of the new generation anticonvulsants, is rapidly gaining popularity in view of both its efficacy and its favourable drug profile. It also acts on the GABA pathways, by inhibiting GABA transaminase (an enzyme involved in the metabolism of GABA) thus increasing CSF concentration. It was first brought to clinicians' attention in 1991 by Chiron[87] et al who reported complete cessation of seizures in 43% of patients. The effect was seen rapidly, often within one week. Subsequently there have been preliminary trials, open and uncontrolled, on the use of vigabatrin in IS showing similar control to that seen with steroids. There is also increasing evidence that vigabatrin is particularly efficacious in the treatment of IS in the group of children suffering from TSC. Acairdi[88] found in his review of 192 patients that out of the 28 patients with TSC, 27 (96%) had complete cessation of their spasms. There has also been one study[89] comparing vigabatrin with steroid therapy specifically in this subgroup of patients. They found that 11/11 responded to the vigabatrin and only 5/11 to hydrocortisone. Again they concluded that vigabatrin might be particularly effective in treating children with both IS and TSC.

Although vigabatrin has only been used in the treatment of IS for a few years, it had been thought to have few side effects. The most commonly reported problems were drowsiness, vomiting and behavioural changes, all of which resolve on discontinuing the drug. There had also been one reported event of myoclonus, though it is not clear whether this was an effect of the vigabatrin or the child's underlying neurological disorder[88].

However, more recently there have been reports of both asymptomatic and symptomatic visual field defects with loss of peripheral vision to varying degrees in adults treated with vigabatrin[90] (see later).

Second line drugs include:

Benzodiazepines, for example, nitrazepam and clonazepam, have been shown to be effective in treating IS but are rarely used as first line monotherapy, they are more

commonly used in addition to, or after failure of other drugs. They are thought to act by acting directly on GABA receptors at chloride channels within the brain. Driefuss et al[91] were the first to report the use of nitrazepam in a controlled study against steroids in 1986, although it had been in use for many years before. They reported that both treatments resulted in a significant reduction in seizures but that the difference between treatments was not significant. The main problems with benzodiazepines that have limited their use are; sedation, excess bronchopulmonary secretions and the development of tolerance in a significant proportion of infants.

Intravenous gammaglobulins came into vogue in the early 1990s. With the knowledge of the favourable effect of steroids it was postulated that there might be an immune mechanism at work and IV gammaglobulins were tried[92]. But in view of their expense, inconvenience and potential problems with infection (contamination with HIV and Hep C was of great contemporary concern) as well as failure of any studies to prove their efficacy, they are now rarely used.

Thyrotropin-releasing hormone (TRH) is widely distributed throughout the brain acting as either a neurotransmitter or neuromodulator. A Japanese study, carried out in 1987[79] showed that just over half of the patients responded to TRH - similar results to those achieved by ACTH. They also noted a lower incidence of side effects in the TRH group. Despite these preliminary findings, it is not yet routinely used in the treatment of IS. The mode of administration (intravenously) and cost (approximately seven times that of ACTH) make the treatment unattractive.

Pyridoxine under went several studies[93] [94] during the late 80's to assess it's validity in treating IS following the successful treatment of vitamin B6 - dependent seizures in the new-born with high doses of pyridoxine and whilst there is no doubt that it is effective in a small number of cases, none of the studies proved that it has such a benefit as to deserve consideration as first-line monotherapy in this disorder. It is however used in Japan as first line treatment.

Epilepsy surgery: Alongside the increased use of vigabatrin for IS there has also been a steady rise in the number of patients undergoing epilepsy surgery. Although the numbers have been small, early results have been promising. In one study[95] of 23 patients only four

failed to respond to surgery. However, these patients were selected on strict criteria suggesting a focal cause and in many children with TSC there are multiple active or potential epileptic foci such that surgery is not thought to be an option. In addition long-term follow up studies have not been undertaken, but in surgery used for other forms of epilepsy the relapse rate is high.

Table six – summary of the pharmacological treatment of infantile spasms

Drug	Comments
First line drugs	
Vigabatrin	If the infant is known to have TSC, or is at high risk i.e. has a first-degree relative with TSC, at the time of onset of the spasms then vigabatrin should be the drug of choice.
Prednisolone	Infants who are commenced on steroid therapy should be admitted for the initial 48 hours of treatment. During this admission their blood pressure should be measured twice daily and their urine dipsticked to exclude the development of hypertension and diabetes respectively. They should then be reviewed on a weekly basis to monitor their blood pressure, urine and weight.
ACTH (Synacthen)	
Second line drugs	
Nitrazepam	
Clonazepam	
Valproate	BEWARE of thrombocytopenia at high dosage.
Trial of **Pyridoxine**	A test dose should be given intravenously alongside EEG monitoring. If the hypsarrhythmia resolves then oral pyridoxine should be tried to see if the spasms resolve.

Prognosis

The long-term prognosis is poor. Few studies have specifically looked at long term out-come. In a study carried out by Riikonen[96] looking at adults with a history of IS, only 17% attended mainstream school, and less than 10% were married, had children or were employed. One fifth had progressed to developing Lennox Gastaut syndrome with severe epilepsy and a further third of patients had continued to have seizures in adult life. Another study[97] looking at the long term prognosis in 162 patients, found mental retardation in 78% and physical handicap in 56%. Only 10% of their children attended normal school.

Conclusion

Although the improvement of diagnostic techniques has led to better recognition of the underlying causes and pathology of IS, response to treatment remains disappointing. Even with the best therapies available abolishment of seizures only occurs in two thirds of patients at best, with a high risk of relapse of spasms and other seizure types and the long-term prognosis is appalling. There are many questions that remain with regard to determining the best treatment for IS.

- **Is one treatment better than another in reducing the long-term morbidity of IS?** It could be argued that long-term psychomotor development is the most important outcome factor for these children. Although the spasms may be distressing in themselves, in a significant minority they resolve spontaneously if left untreated, though many children will go on to develop other types of epilepsy. However, the vast majority will develop severe learning difficulties. Although it is thought that earlier control of the spasms may improve outcome, no study has specifically considered this and no study has set out to compare different therapies with regard to long-term outcome.
- **Is there an optimum steroid dosage regime?** There is currently no widely accepted dosage regime for steroid dose, frequency, duration or type of steroid used in the treatment of IS. The studies in the literature have used many different regimes but none have been large enough to give reliable results.
- **Is vigabatrin really the drug of choice for patients with TSC or for those at a high risk of TSC at the time of diagnosis their spasms?** Only one study[89] to date has considered the use of different drug regimes in the treatment of the subgroup of patients who have IS as a result of TSC. Their results suggested that vigabatrin was more efficacious in this group than steroids, however their numbers were small (22 in total).
- Finally, if IS can be prevented from occurring in infants with TSC will this reduce the incidence of severe learning difficulties and the development of other seizure types in this subgroup?

In order to try and answer the first question it was decided that a large trial needed to be set up to look at the effect of treatment in terms of both seizure control and more importantly long-term psychomotor outcome. It was decided that this would be a pragmatic drug trial comparing the two drug treatments currently in widespread use in the UK; adreno-corticoid or hormonal treatments which I will call "steroids" for convenience and vigabatrin. However, it is possible that adrenocorticotrophin hormones work not by production of steroid hormone through stimulation of the adrenal cortex but by direct negative feedback on the hypothalamus reducing ARH products. This theory promoted by Dr Baram suggests that ARH is epileptogenic at a critical period in brain development. This brought up the next two important questions; which steroid dosage regime should be used in the trial? and

if there were enough evidence to suggest that patients with TSC had a better response to vigabatrin, should this sub-group be excluded from the trial?

There are currently two preparations of steroids widely used in the treatment of IS in the UK

- Prednisolone given orally.
- Adrenocorticotrophin hormone (synacthen) given as an intramuscular (IM) injection.

It was decided that both drugs would be used in the trial as many doctors who would be recruiting into the trial expressed that they thought one type to be superior to the other, although these opinions are not founded on evidence based medicine. There has only been one double blind, randomised crossover trial comparing ACTH and prednisolone. This study by Hrachovy[73] used lower doses of both ACTH (20u/day) and oral prednisolone (2mg/kg/day) than usually used in the UK and found no significant difference between the two different types of steroids. Five out of twelve patients responded to the ACTH and four out of twelve to the prednisolone, but the numbers of patients enrolled into this study were small and will have been insufficient to detect a clinically important difference in response. The next question to be addressed was the dosage to be used for each of the steroids. Again only one controlled trail comparing high dose versus low dose ACTH had been reported[72] and the numbers were small but no difference was found between the two groups. We therefore had a dilemma; if we were going to conduct a large clinical trial we wanted to ensure that we were using an adequate dose of ACTH; one which would give us the best clinical response, but on the other hand high dose steroids may be associated with more frequent serious side effects. In the one paper that had looked at the side effects of ACTH use in IS in detail[83] all the deaths had occurred in children who had received very large doses i.e. over 100 units ACTH given two times a week. It was therefore decided that a reasonable dose of ACTH would be 40 units on alternate days increasing to 60 units if no response was seen within a week, a dosage regime currently in widespread use in the UK, but the duration of treatment was restricted to 2 weeks since length of treatment as well dosage seemed to bear a significant relation to the incidence of side effects.

Deciding the dose of prednisolone to be used proved more problematic. Again we wanted to ensure that we were using an adequate dose that would give us the best clinical response but without causing serious side effects. Historically, large doses of prednisolone have been used when treating children. In the 1970's doses were reduced, often to 2mg/kg body

weight probably as a result of a wish to be logical over the treatment and because of concerns over the systemic side effects, although there was no scientific data to suggest that a reduction was necessary or that a dose on a per kg basis was logical. Large doses of steroids have been given for many years to pregnant women with no known ill effect to the foetus. High doses well above 2mg/kg are used in acute asthma attacks in children, albeit for only a few days. There are several pathophysiological mechanisms to explain why it might be safe to give relatively large doses of steroids to young children, including a relatively large volume of distribution. In the adult and older child only the kidney inactivates cortisol and prednisol. In the infant they are metabolised in every organ of the body, thus giving an extensive first pass metabolism effect throughout the first year which tails off after the first three months of life (personal communication). It was therefore thought that although 2mg/kg was the most widely reported dose of prednisolone for infantile spasms it might be inadequate. Baram[71] et al in a single blinded study used a high dose of ACTH (150u/m^2/day) against a low dose of oral prednisolone (2mg/kg/day), concluding that ACTH was more effective in terminating infantile spasms. Fourteen out of fifteen patients responded to the ACTH whereas only four out of fourteen responded to the relatively low dose prednisolone perhaps suggesting that when smaller doses of the steroids were used fewer patients responded. We would suggest that if these studies were to be repeated on a larger population using higher doses of prednisolone a greater proportion of infants might show a response. Their response to ACTH also helped to justify a high dosage regime.

Higher doses of oral prednisolone had been in use at the Royal United Hospital (RUH) during the previous thirteen years. We decide therefore to look at the patients who had been treated with prednisolone for infantile spasms during this time in order to try and assess the efficacy and safety of high dose oral prednisolone (usually 20mg tds for two weeks, regardless of weight or age) in the treatment of IS.

The treatment of infantile spasms with high dose oral prednisolone: a retrospective review.

Aims

In this retrospective study, the aims were to identify the frequency and type of side effects suffered by infants being treated with high dose oral prednisolone, in particular those that could be considered to be potentially serious or life threatening, and to observe the effect of the high dose prednisolone on the spasms themselves.

Patients and methods

The study group comprised all patients who had been admitted to the RUH between January 1983 and August 1996 with a diagnosis of IS. Patients were collected by two methods. Those who had been admitted between August 1987 and August 1996 were located via a database at Bath Health Information Services and those admitted prior to August 1987 were located via the EEG departmental records.

The medical notes were then retrieved and reviewed. Both a clinical description of the spasms and an EEG recording compatible with West syndrome (i.e. hypsarrhythmia or modified hypsarrhythmia) were required to fulfil the criteria for a diagnosis of IS. The following information was then sought for each patient;

- predisposing factors,
- age at diagnosis of IS,
- the apparent time delay from onset of spasms to diagnosis,
- time to start of treatment,
- dose and duration of steroids and the effect of treatment on spasms.

The notes, including nursing profiles, observation charts etc. were then scrutinised for any evidence of side effects suffered during the treatment, including;

- hypertension,
- glycosuria,
- intercurrent infections.

Results

21 patients in total were identified has having IS during the period of January 1983 to August 1996. In our study there were 10 girls and 11 boys.

There were four sets of notes in which the nursing observation charts had been lost and one further set only had the clinic letters available for the period of time that the patient suffered the IS (patient 21).

The age at diagnosis of the spasms ranged from three to 18 months with a mean of eight months and a median of seven and half months; no significant age difference was seen between girls and boys. In seven of the patients, no underlying cause was found. There was a wide range of predisposing factors in the remaining fourteen patients (table seven).

Table seven

Predisposing factors	**Number of patients n = 21**	**Symbol denoting this diagnosis in table 8**
None (Idiopathic)	7	*
Neonatal hypoxic ischaemic encephalopathy	5	A
Down Syndrome	2	B
Tuberous Sclerosis	1	C
Head Injury	1	D
Developmental delay (unspecified)	1	E
Polymicrogyria	1	F
Lisencephaly	1	G
Unknown	1	H
Idiopathic but time related to Pertussis Vaccination	1	I

One third of the patients had no cause underlying their IS i.e. they were idiopathic in type. Five of the patients had a history of birth asphyxia and one of developmental delay prior to the onset of spasms.

14/21 of the patients received 20mg prednisolone tds the other seven received slightly lower doses (table eight).

Table eight

	Age at Diagnosis	Delay to Diagnosis	Dose of oral prednisolone	Time to Stop spasms	Relapse	Other drugs used
1. [a]	9 months	1 week	20mg tds 1 month then stopped	3 days	None	None
2. [f]	5 months	2 months	20mg tds 2 weeks then weaned off	8 days	None	None
3. *	5 months	5 days	20mg tds 2 weeks then weaned off	3 weeks	None	None
4. [b]	5 months	6 weeks	20 mg tds 2 weeks then weaned off	2 weeks	None	None
5. *	8 months	5 weeks	20mg tds 2 weeks then stopped	1 day	None	None
6. [d]	7 months	4 days	10mg tds 2 weeks then weaned off	5 days	None	None
7. [g]	4 months	3 days	15mg tds 2 weeks then weaned off	2 weeks	None	None
8. [a]	8.5 months	3 weeks	10 mg tds 2 weeks then weaned off	2 weeks	None	None
9. *	9 months	9 months	10 mg bd 2 weeks then weaned off	reduced	N/A	Nitrazepam
10. [a]	6 months	3 months	20mg tds 2 weeks then weaned off	Reduced	N/A	Nitrazepam
11. [h]	6 months	2 months	20mg tds 2 weeks then stopped	Reduced	N/A	Vigabatrin, clonazepam, Valproate
12. *	15 months	8 months	20 mg bd 4 weeks then weaned off	Reduced	N/A	Nitrazepam, CMZ
13. *	8 months	2 months	20mg tds I month then weaned off	1 day	Yes	Vigabatrin, Nitrazepam, Valproate, Pyridoxine, Biotin
14. [a]	3 months	1 month	20mg tds 2 weeks then weaned off	10 days	Yes	Vigabatrin, Valproate
15. [c]	7 months	4 months	20mg tds 1 month then weaned off	2 days	Yes	Vigabatrin
16. *	10 months	6 weeks	20mg tds 2 weeks then stopped	3 days	Yes	Clonazepam, CMZ
17. [c]	6 months	1 month	10mg qds 1 month then weaned off	6 weeks	Yes	Nitrazepam
18. *	5 months	1 week	20mg tds 2 weeks then weaned off	4 days	Yes	Steroids repeated fits stopped next day, no further relapse
19. [b]	11 months	6 months	20mg tds 2 weeks then stopped	Didn't	N/A	Vigabatrin, Valproate, Nitrazepam
20. [a]	11 months	Unknown	20 mg a day 2 weeks then stopped	Didn't	N/A	Valproate, Nitrazepam, CMZ Clonazepam, ethosuximide
21. [e]	18 months	Unknown	20mg tds 2 weeks then weaned off	Reduced	N/A	Steroids repeated, Vigabatrin and Valproate

- **idiopathic, [a] birth asphyxia, [b] Down syndrome, [c] tuberous sclerosis, [d] head injury, [e] developmental delay, [f] polymicrogyria, [g] lisencephaly, [h] unknown, [i]pertussis vaccination. See table seven for diagnoses.**
- **In patient 17 it is not clear whether the cessation in spasms was directly due to the steroid therapy or nitrazepam but analysis was performed on an intention to treat basis.**

Table to show the age at which the infantile spasms were diagnosed and the delay from onset of the spasms to their diagnosis. The dose and duration of oral prednisolone, the effect it had on the spasms and any other drugs used.

Nineteen (90%) of patients showed either a reduction in the number (5) or complete cessation of their spasms (14) as a result of prednisolone treatment with four of the fourteen receiving less than 20 mg tds. Two patients had no response to the prednisolone, both were treated with a wide variety of drugs, with no response and both went on to develop further types of fits. Six of those that responded subsequently relapsed after stopping the prednisolone, one initially receiving 10mg tds only: one was given and responded to a second course of prednisolone.

In five patients the number of fits were reduced by prednisolone, in two of the patients the fits were further reduced by the addition of nitrazepam and in one by vigabatrin, the remaining two received a variety of drugs including vigabatrin, clonazepam and valproate with no beneficial effect.

Side effects

In eight of our patients no side effects were reported. Irritability was by far the commonest problem experienced by eight of the patients, drowsiness, changes in appetite and poor sleeping were also experienced. Diarrhoea and vomiting occurred in two of the patients requiring oral rehydration only. No other infections were reported during the use of steroids. A transient mild rise in blood pressure was noted in three patients but no medical intervention was required and in each case the blood pressure returned to normal after the course of steroids was completed. In a fourth patient (patient 21) the blood pressure was noted to be high 150/90 at follow up: this child's notes were missing but in subsequent letters the systolic pressure is recorded as 100 after the steroids had been tailed off.

Table nine

Side effects (n=21)	No. Of patients
Irritability	8
Drowsiness	3
Transient rise in BP	3 + (1)
Diarrhoea and vomiting	2
Cushingnoid	3
Increased appetite	2
Decreased appetite	1
Poor sleep	1

In eight patients no side effects were reported, in the remaining 13 patients one or more side effects were experienced.

No glycosuria was recorded at any time in any of the patients. Finally cushingnoid features were noted in three of the infants, two of these patients had received two courses of steroids (table nine).

Discussion

This was a small retrospective study and is therefore prone to bias. It is possible that cases were missed the collection method and it is possible that those patients may have had a worse outcome. The estimated incidence of IS ranges from 0.16 - 0.42 per 1000 live births per year[50 51 52 53]. In the Bath district there are just over 5000 live births per annum. We would therefore expect to see on average one to two cases a year (i.e. 13 -26 cases over the 13 year period). We believe that using our search strategy we are unlikely to have missed many cases. In addition the study is prone to selection bias (see chapter five), that is patients who might respond less well to steroids may have been given an alternative treatment. Finally the numbers are small, thus the power of the study is small.

The side effects of steroids are well known. One of the aims of this study was to ascertain the frequency of serious side effects with the use of high dose oral steroids. In our small study of 21 patients none suffered serious complications of steroid therapy. There are the less serious side effects that are often transient but nevertheless cause a certain amount of morbidity such as hypertension. In our group we had three patients who had a mild transient rise in blood pressure (95/50 to 155/80, 100/60 to 140/80 and 105/70 to 160/70), fortunately with no serious sequele. The hypertension was usually seen after the patient had been discharged from hospital, whilst being followed up in the out patient clinics. Hypertension is often overlooked and as a result the amount of information available in the literature is lacking. In the study carried out by Riikonen and Donner[83] looking specifically at the side effects of ACTH only 17 out of 162 patients had their blood pressure routinely measured and in a review of the treatment by child neurologists of infantile spasms by Bobele and Bodensteiner[53] only two thirds measured blood pressure on a weekly basis during treatment. In our study the blood pressure had been monitored in all patients for whom the full medical notes and nursing observation charts were available. In our study two thirds of the patients complained of minor side effects although none were sufficiently severe to prevent continuation of the therapy.

Control of fits occurred in the majority of our patients and of the patients in whom fitting was not controlled by a course of prednisolone, other anticonvulsants including vigabatrin also failed. We would speculate that our success rate of 70% complete remission may be due to our larger than generally accepted dose of 20mg three times a day, regardless of age or weight (however the lower doses used in some patients were also effective). This finding has not been previously published but does show, importantly, that higher doses of prednisolone are effective.

It is interesting to note that in our study the patients who had idiopathic infantile spasms (denoted by * table eight) faired no better or worse in terms of outcome of seizures. The one patient known to have TSC showed a good response to steroids initially but subsequently relapsed and was successfully treated with vigabatrin.

In retrospect many of the patients were thought to have had the spasms for some time prior to diagnosis. The time delay to diagnosis ranged from one week to nine months (table eight). Often this was because the spasms had been misdiagnosed, for example as colic, but in others the parents had not sought medical advice. In one patient, the spasms were diagnosed when the patient attended clinic for a different reason at the age of nine months. The mother stated that the spasms had been present from birth but that she thought they were normal for her child. This highlights the great difficulty in diagnosing this syndrome early.

Conclusion

In conclusion, we found high dose oral prednisolone to be an effective treatment for IS, stopping seizure activity in two thirds of the patients treated. In addition, life-threatening complications did not occur with high dose prednisolone in our group suggesting that they may be infrequent in this effective regime for West syndrome. Although minor side effects are commonly experienced these are transient and cause no long-term morbidity. We therefore decided that it was justified to use high dose oral prednisolone in order to achieve maximum effect in our trial. The core group decided on a dosage regime of 40mg / day increasing to 60mg / day if no effect was seen after one week, in the hope that not all infants would need 60/kg/day and that starting at a lower dose would encourage participation by parents and doctors in the trial.

A review of vigabatrin in the treatment of infantile spasms in tuberous sclerosis complex.

The next question to be addressed was whether patients known to have a diagnosis of TSC at the onset of their spasms should be included or excluded from the trial. We therefore undertook a review of the English literature to examine the efficacy and safety of vigabatrin in the treatment of IS in infants suffering from TSC.

Methods

A Medline and Embase search dating back to 1990 of the English literature for all studies investigating the effect of vigabatrin on IS was performed. Vigabatrin was first brought to clinicians attentions by Chiron in 1991 and it is unlikely that there are any relevant trials published prior to 1990. All references in the articles cited were then examined for further references. Studies that did not distinguish which infants had an underlying diagnosis of TSC were excluded.

Results

Fifteen studies investigating the effect of vigabatrin on IS were found in total. Of these, ten studies gave a breakdown for the effect in patients with TSC in addition to the overall results. Two of these studies[98 99] were then rejected because the patients were all included in a further publication[100].

Table ten

Study	Type of study	No patients	M:F
Chiron et al 1990[101]	Single Blind	45	Not given
Chiron et al 1991[87]	Open add on	70	33:37
Appleton et al 1993 [100]	Retrospective	21	10:11
Vles et al 1993[102]	Open	6	2:4
Schmitt et al 1994[103]	Open	17	Not given
Vigevano et al 1995[104]	Open randomised	21	Not given
Aicardi et al 1996[88]	Retrospective	192	109:83
Chiron et al 1997[89]	Open randomised	18	5:6

Table of authors of the studies reviewed, the type of study, the total number of patients treated with vigabatrin and the male to female ratio of patients, presented chronologically.

There were five open prospective studies, two retrospective studies and one single blinded study. The total number of patients in each study ranged from as few as six to as many as 192. The male to female ratio was only included in five of the studies and overall showed a slight male preponderance of 1.1:1.0 (table ten).

The average age at treatment was given for five of the eight studies with an overall average of 9.9 months. In five of the studies the patients had received therapy prior to the vigabatrin and in three of these studies the patients continued with concurrent therapy alongside the vigabatrin. The dose of vigabatrin varied from 50 to 200mg/kg/day (table eleven).

Overall there were 390 infants treated with complete cessation of spasms occurring in 242 i.e. 62%. Of these 77 had a known underlying diagnosis of TSC, the remaining 313 had IS due to other causes or no cause found at the time of the study. 73 (94%) of the patients with TSC had complete cessation of their seizures as compared with 169 (54%) of the remaining patients (table twelve).

Table eleven

Study	Av. Age (months)	Previous Treatment	Concurrent Treatment	Dose of vigabatrin (mg/kg/day)
Chiron et al 1990[101]	26	Yes	Yes	50 – 200
Chiron et al 1991[87]	Not given	Yes	Yes	50 – 200
Appleton et al 1993[100]	8.5	No	No	80 – 120
Vles et al 1993[102]	4.75	Yes	No	50 – 100
Schmitt et al 1994[103]	Not given	Yes	Yes	Up to 150
Vigevano 1995[104]	4 –9 months	No	No	100 – 150
Aicardi et al 1996[88]	5.8	No	No	20 – 400 (Av 99)
Chiron et al 1997[89]	7.25	Yes	No	150

Table showing the average age at treatment, whether previous treatment had been given, whether concurrent treatment was given and the range of doses of vigabatrin administered.

Three [101] [102] [103] of the papers did not specify the time taken to achieve cessation of the spasms and a further paper[87] specified that cessation had occurred within a month of commencing the vigabatrin. Appleton[100] reported that control occurred within seven days and Vivevano[104] reported control within eight days. Aicardi[88] and Chiron[89] both reported an average of 4 days for control of spasms in those patients who responded to vigabatrin.

Table twelve

Study	Patients with TSC (n=77)		Patients without TSC (n=313)	
	Total number	Number of responders	Total number	Number of responders
Chiron 1990	8	7	37	9
Chiron 1991	14	12	56	29
Appleton 1993	3	3	18	14
Vles 1993	1	1	5	3
Schmitt 1994	2	2	15	5
Vigevano 1995	3	3	18	6
Aicardi 1996	28	27	164	104
Chiron 1997	18	18	0	0
Total	77	**73 (94%)**	**313**	**170 (54%)**

Table showing the response rate to vigabatrin in all the patients, those without tuberous sclerosis and those with tuberous sclerosis. A responder is defined as a patient in whom there was total cessation of spasms.

Table thirteen

Side Effect	No of patients reported in each study								
	Chiron 1990	Chiron 1991	Appleton 1993	Vles 1993	Schmitt 1994	Vigevano 1995	Aicardi 1996	Chiron 1997	Total
Drowsiness		5	2				15	3	25
Behavioural				1			12	3	16
Insomnia		3					5		8
Hypotonia		4		1			4	1	10
Diarrhoea							1		1
Weight gain		4					1		5
Vomiting									0
Other	12	2				3	4	1	22
Total	**12***	**18**	**2**	**2**	None reported	**3#**	**42**	**8**	**87**

***9 children reported adverse events of hyperkinesia, weight gain and drowsiness**

 # specific side effects not stated.

Table showing the number and type of side effects / adverse reactions reported in each study (there were 390 patients in total).

In total 87, adverse events, from the 390 patients were noted (table thirteen). The majority of these were transient and none were reported to continue after stopping the vigabatrin. In all the studies only seven patients were reported as having the vigabatrin withdrawn due to intolerability. The reasons for withdrawal were: hypertonia, hypotonia, hyperactivity, irritability and myoclonus. There were no reported deaths attributable to vigabatrin.

Discussion

This review found a male : female ratio of 1.1:1. The average age of treatment was 9 months, which reflects that many of the patients had been tried on more traditional therapies such as steroids before vigabatrin was used. Interestingly, in past studies TSC has accounted for approximately 10% of patients with IS. In these studies it accounted for 20% of the patients. This may be due to biased selection of patients (as most of the studies were either open or retrospective) or alternatively with improving imaging and diagnostic techniques, it may be that more patients are being diagnosed as having TSC. It may be a chance finding.

The group of patients with TSC treated with vigabatrin had a 94% response rate. This response rate was seen in spite of resistance to other treatment and delay in commencing therapy. In contrast, in the group of patients in whom there was no history of TSC, the overall response rate (i.e. total cessation of spasms) to vigabatrin was 54%, similar to steroids but, it must be remembered that many of these patients treated with vigabatrin were not newly presenting and had previously failed to have their spasms controlled by other therapies.

Many children who suffer IS ultimately go on to have further seizures. The second commonest seizure type in young children with TSC is partial seizures. Although partial seizures are generally considered to be resistant to treatment with vigabatrin, a recent study by Nabbout et al 1997[105] suggested that in children with TSC vigabatrin may be effective in treating partial seizures in up to 85% of patients.

Various dose regimes were used, but the core group decided to use the licensed dosage regime:

50mg/kg/day orally in two divided doses for 24 hours (i.e. a total of two doses), increasing to 100mg/kg/day orally. If seizure control is not achieved then the dose can be further increased to a maximum of 150mg/kg/day in two divided doses.

Although vigabatrin has only been in clinical use for a few years, it appeared to have few serious side effects. Although a total of 87 adverse events were reported in the studies reviewed, only seven patients had their vigabatrin stopped and no side effects were reported to persist after withdrawal of the vigabatrin. (The reasons for withdrawing the vigabatrin were only given for five of the seven patients and were: hypotonia, hypertonia, hyperexcitability, irritability and myoclonus).

Earlier primate studies in dogs and rats had suggested a risk of intramyelinic oedema with vigabatrin, but serial evoked potential studies and reports of brain histology in treated patients have not supported this effect in humans[106]. However, since this work was completed there have been reports of both asymptomatic and symptomatic visual field defects with loss of peripheral vision to varying degrees in adults treated with vigabatrin[107] [108]. It appears to occur most commonly in patients who have been treated with vigabatrin for several years and more recent research, at least in adults, suggests that it is not reversible on withdrawing the vigabatrin[109]. Out of approximately 140,000 adults treated with vigabatrin between its introduction in 1989 and 1997 there had been 28 reports of visual defects - a frequency of less than 0.1[90 107 108 109]. The main difficulty in infants is that they cannot be tested or monitored for visual field defects (a child needs to be at least eleven to be able to co-operate and complete the test). However, on balance the devastating effects of IS probably outweigh the risks of developing visual field defects (which may be asymptomatic): a paediatric advisory group[110] have recommended that vigabatrin should still be prescribed for IS, and the medicine licence in the UK remains. In addition it must be remembered that refractory epilepsy may cause visual defects itself, for example by disseminated intravascular co-agulation (DIC) occurring with prolonged seizure activity[111] and other anticonvulsants such as sodium valproate and phenytoin have also been associated with visual defects[112]. In some patients with infantile spasms, their underlying disease may also cause visual field defects. Further research into the effects of vigabatrin on visual fields in this group of children is required. Unfortunately, because of the

difficulty in testing visual fields in young children, it may be necessary to wait several more years until infants treated with vigabatrin for infantile spasms become old enough to co-operate with such testing. In addition, because of the devastating effect that the spasms can have on development many of these children may never be able to perform visual field testing.

Unfortunately only tw`o of the studies gave a breakdown for the effect of vigabatrin on cessation of spasms due to other underlying aetiologies (e.g. cerebral dysgenesis, birth asphyxia), a total of only 15 patients, so it is not possible to comment on the efficacy of vigabatrin in these other subgroups. Neither is it possible to discuss the effect of vigabatrin on EEG appearance in this review as the papers did not contain sufficient information. It is also known that abolition of hypsarrhythmia on EEG can lag behind the clinical response, and some of the studies only had a relatively short follow up period.

Conclusion

We conclude that vigabatrin should be considered the drug of choice for patients with IS and either a known diagnosis of TSC, or at high risk of TSC before investigations are complete i.e. those with a first degree relative with TSC because of its efficacy, speed of onset and relatively safe drug profile. Paradoxically, steroids despite the side effects may be a better choice for the remainder, but further information is required and a randomised controlled trial clearly justified.

On the basis of this review it was decided that it would be unethical to randomise patients with, or at high risk of TSC to steroids and they would therefore be excluded from the trial.

CHAPTER FOUR

The United Kingdom Infantile Spasms Study (UKISS)

Appendix one – protocol and trial pack

A core group (appendix two) was identified to propose a study design to investigate the use of "steroids" and vigabatrin in the treatment of infantile spasms to try establish the most effective initial treatment regime for this serious disorder. At the time of designing the study the two "steroid" preparations in widespread use in the UK were ACTH (adrenocorticotrophin hormone) and prednisolone. ACTH was a natural product derived from a bovine source and as discussed above was administered as a daily intramuscular injection with a commonly accepted dosage regime of 40-60iu/day. However, with the existing concerns surrounding bovine spongiform encephalopathy (BSE) ACTH was withdrawn from the market. It was replaced with synacthen depot, a synthetic analogue of ACTH with a dose equivalent of 0.5-0.75mg/alternate days.

Infantile spasms are relatively uncommon and in order to be able to recruit the numbers required to give the study reasonable power, the trial would need to recruit infants from a large population such as the whole of the UK rather than just a few health districts. In order to try and minimise selection bias it was decided that the trial should be a randomised controlled trial with concealment of allocation (see chapter five). Ideally, in order to minimise performance bias (see chapter five) the trial should also be blinded so that the patients (parents/guardians) and medical staff administering the treatment and measuring outcome would be unaware as to which treatment the subject had been randomised. However, this would be problematic because synacthen depot can only be given by intramuscular injection whilst prednisolone and vigabatrin are administered orally; nowadays it is generally considered unethical to administer placebo injections to young infants. In addition, the side effects of steroids are easily recognised by both clinicians and parents so that it was likely that the treatment that had been assigned would become apparent in a significant number of cases. The final dilemma was that few placebo controlled trials have been performed and those that have contain insufficient number of patients to provide adequate power to the study, so that we do not know if any one treatment is more effective than no treatment at all. However, many would argue that delaying treatment (which might worsen the outcome) by administering a placebo

treatment is also unethical. It was therefore decided that this should be a national, multicentre, randomised, parallel-group, open clinical trial.

The trial centre would be in Bath and one Paediatric Neurologist in each of the old Health Regions would be identified and recruited to help promote the study. It was hoped that every health district within the UK would participate. Papers dealing with the epidemiology of IS put the incidence between 1 in 2380 and 1 in 6250 births (see chapter three). The average UK birth rate is approximately 800,000 per year. Therefore it should be possible to recruit between 130 and 340 new cases per year. Taking into account exclusions the scheduling of the study presumed a recruitment rate of approximately 200 per year. Assuming recruitment of 250 children over an 18 month period, with approximately 125 randomised to vigabatrin and 125 to "steroids" and assuming approximately 50% would achieve cessation of seizures in the "steroid" group, the trial would have 90% power to detect an improvement in cessation of seizures to 70% in the vigabatrin group. The consensus of the core group was that an improvement of at least 20% in cessation of spasms would be required to persuade clinicians to change their clinical management of these patients. Central randomisation by telephone call would register the child into the trial, report baseline information and allocate initial treatment (concealed in sealed envelopes). Patients would be allocated to one of two treatment groups: vigabatrin or steroids. The steroid group would then be further randomised to receive synacthen or prednisolone. To try and reduce selection bias further, patients would be stratified before entry according to sex, age and whether they belong to symptomatic or non-symptomatic groups (see later).

We envisaged minimal problems with compliance and loss to follow up. This is a serious disorder with profound sequele. The motivation for clinicians and parents of patients to participate in treatment is high. The workload to be imposed on attending physicians would be little more than constitutes good clinical practice. The workload to be imposed on parents is small. Patients known to be likely to move outside the country during the trial period would be excluded at entry. As this would be a national study, movement within the UK should not lead to loss of contact. Patient's NHS number would be recorded on entry to the trial thus making subsequent identification easier. In a previous multicentre follow-up study conducted from Bath of 276 children, the investigators achieved 97%

follow-up at 3 years and 9 months. It was hoped that we could achieve a similar or improved rate of follow-up in the UKISS trial.

To maximize the amount of information gathered during the trial it was decided to set the drug trial within an epidemiological report of all cases of infantile spasms occurring within the UK. This would allow us to collect further information on the epidemiology and natural history of infantile spasms, including those infants who would be excluded from the drug trial for whatever reason. It was decided therefore that we would ask that all cases of infantile spasms would be reported to the trial centre even if the individual patient was not to be recruited into the drug trial. This would also be helpful in allowing us to ascertain how representative our trial population was compared to the whole UK population. Brief clinical details would be requested.

In order to be recruited into the drug trial the patient would have to be between 2 completed calendar months and 1 year of age (up to but not including their first birthday) at the onset of their spasms. Below the age of two months infantile spasms are rare and can be difficult to diagnose. It was therefore decided that infants under the age of two months would only be eligible for entry into the epidemiology part of the study. It was decided that one year of age would be the upper age limit for drug trial entry for two reasons; firstly, measurement of long-term psychomotor development (see later) would be undertaken when the infant reached 12-14 months; secondly, after the age of one other possible diagnosis should be considered, for example infantile myoclonic epilepsy, that can be easily mistaken for infantile spasms. Infants would be excluded from the drug trial (but not the epidemiology trial) if they were either known to suffer from tuberous sclerosis (TSC) or who were at high risk i.e. a presumptive diagnosis of tuberous sclerosis because of; known affected parent, previously diagnosed cardiac rhabdomyoma, hypomelanic macules, a forehead fibrous plaque or shagreen patch noted, a retinal phakoma seen, or were known to have polycystic kidneys. We recommended that first line therapy in these infants should be vigabatrin (see chapter three). Infants would also be excluded from the drug trail if they had received previous treatment for infantile spasms or had been treated with vigabatrin or steroids within 28 days of the first diagnosis of infantile spasms for any other reason. This was because the aim of the trial was to establish the most effective initial treatment for infantile spasms. Other exclusion criteria included; infants with a contra-indication to vigabatrin or steroids; infants with a lethal or potentially lethal other condition; inability of

parents or guardians to give informed, signed consent; inability of parents or guardians to know when spasms stop - to the nearest whole day; infants expected to leave the UK within one month of randomisation and finally any infants enrolled in a concurrent trial that either uses therapy that might affect the outcome measures of the UKISS trial or one that is time/effort consuming for the patients/guardians or the infants' medical practitioners.

The trial would then be discussed with the parents or guardians and their consent requested for participation in the trial. If consent was refused for entry into the drug trial or the infant was excluded for any reason given above then consent would be requested for entry into the epidemiology trial only. If consent into the drug trial was successfully obtained then an EEG (or video EEG) would be obtained as quickly as possible to confirm the diagnosis of infantile spasms and allow randomisation into the drug trial. If the EEG was normal the child would be excluded from the drug trial (but not the epidemiology trial). Prior to randomisation for entry into the study the children would be stratified for; gender, male or female; by age, 60 to 119 days, 120 to 179 days, 180 to 239 days, 240 days and over; whether the infant belonged to a symptomatic or non-symptomatic group. The symptomatic group consisted of those infants known to have an underlying diagnosis such as a proven chromosomal abnormality, a syndrome diagnosis, cerebral palsy or a diagnosis of neonatal encephalopathy with seizures, and those with a diagnosis of delayed development having already been made by either a medical practitioner or health visitor before the onset of the spasms. The non-symptomatic group includes all infants who had no known underlying diagnosis at the time of diagnosis and who had normal development prior to onset of the spasms. The purpose of pre-randomisation stratification was to balance the treatment groups with respect to factors, which were identifiable at randomisation that might affect the outcome measures.

All children eligible for the trial would then be randomised into the two treatment groups; vigabatrin or "steroids" and all patients randomised to receive "steroids" would undergo a second randomisation; to receive either synacthen depot or prednisolone. The only pharmacological intervention for the infantile spasms for the initial trial period of two weeks would be the drug to which each patient had been randomised. Those randomised to receive vigabatrin would be given the dosage regime recommended by the manufacturers: 50mg/kg/day orally in two divided doses for 24 hours (i.e. a total of 2 doses); then to

increase to 100mg//kg/day orally in two divided doses in all patients; if at 96 hours seizure control has not been achieved then the dose should be further increased to 150mg/kg/day orally in two divided doses; they would then continue on this dose (100 or 150mg/kg/day) until the time of their final developmental assessment around 12 - 14 months of age unless no response or relapse occurred (see below). As ACTH gel was no longer available in the UK, synacthen depot was substituted at the equivalent dosage; 0.5 mg on alternate days (equivalent to 40iu/day of synacthen) intramuscularly (regardless of age or weight) for two weeks. If at the end of the first week seizure control had not been achieved then the dose would be further increased to 0.75 mg on alternate days (equivalent to 60iu/day of synacthen) intramuscularly. This is a relatively high dosage regime, but one that is widely accepted by clinicians in the UK. It is important that exogenous steroids are not stopped suddenly, especially if they have been administered at high doses, as sudden withdrawal can lead to an Addisonian crisis.

Addisonian Crisis

Addisonian crisis is acute adrenocortical failure that may occur as the result of sudden withdrawal of exogenous steroids, and is a critical medical emergency. Delay in treatment may result in death. The patient usually presents with abdominal pain, vomiting, diarrhoea, pyrexia, dehydration and profound hypotension and later with collapse and coma. Laboratory parameters show low sodium, bicarbonate, glucose and cortisol levels and high potassium, urea and endogenous ACTH. Immediate management consists of resuscitation and intravenous hydrocortisone. All patients on steroid treatment should be advised not to alter their drug regime except on medical advice and should carry a medi-alert card.

This group would therefore tail on oral prednisolone over 15 days. Those on 0.5 mg on alternate days of synacthen depot would receive 30mg of oral prednisolone for 5 days, then 20mg for 5 days then 10mg for five days and stop. Those on 0.75 mg on alternate days of synacthen depot would receive 40mg of oral prednisolone for 5 days then 20 mg for 5 days then 10mg for 5 days then stop.

Those randomised to prednisolone would be given 10mg qds. orally (regardless of age or weight) for two weeks; if at the end of the first week seizure control had not been achieved the dose should be increased to 20mg tds. orally. The dosage regime is higher than that frequently used by clinicians in the UK but was chosen for the reasons outlined in chapter three. This group would also tail on oral prednisolone over 15 days. Those on 40mg (10 mg qds.) would reduce to 30mg for 5 days, then 20mg for 5 days then 10mg for five days and stop. Those on 60mg (20 mg tds.) would reduce to 40mg for 5 days then 20 mg for 5 days then 10mg for 5 days then stop.

Primary outcome measure

The primary outcome measure would be the number of patients who achieve complete cessation of spasms for at least 48 hours up to and including the end of the 14th day of treatment.

At enrolment the parents/guardians would be given their copy of a 'fit diary' and its use fully explained to them. The parents/guardians would be asked to make a once daily entry for the first 4 weeks of the trial and a once weekly entry thereafter, until the time of the final developmental assessment (12 -14 months), with a final 7 day daily entry for those still having seizures.

Responders are defined as those in whom there is total cessation of spasms for at least 48 hours up to and including the end of the 14th day of treatment.
Relapse: a single spasm in a responder constitutes a relapse.

If a child relapses within the initial two week period then the lead clinician would be expected to increase the dose of the initial therapy up to the maximum recommended dose as per protocol.

The patient should be seen by the enrolling physician at two weeks post-trial entry to confirm their progress. If the infant has responded the patient will continue on the same therapy as above. The trial will be analysed by intention to treat at the time of randomisation; in order to minimise the effects of a multitude of different subsequent treatments if a response has not occurred after 2 weeks, the lead clinician will be asked to change to the alternative therapy i.e. either steroids after vigabatrin (the lead clinician to choose which steroid – synacthen depot or prednisolone) or vigabatrin after steroids. This alternative treatment will continue for the third and fourth weeks (a full 14 days) at the same dose as recommended for the first two weeks. If both treatments fail, the clinician will be left to choose the most appropriate treatment.

If the patient relapses after the initial two week trial period we suggest that if the child is on vigabatrin to increase the dose in parallel with the child's weight gain (if increase is more than 1 kg) or if on 100mg/kg/day increase to 150mg/kg/day; If on steroids repeat the course once even if tailing. If these measures fail after a full 14 days treatment change to

the alternative therapy i.e. either steroids (synacthen depot or prednisolone) after vigabatrin, or vigabatrin after steroids.

Secondary outcome measures

It was decided that the time taken to complete cessation of all spasms for at least 48 hours would be measured as many clinicians believe that the quicker the spasms are brought under control the better the long-term outcome. If one treatment does bring the spasms under quicker control and also improves long-term psychomotor development then this would support the above hypothesis. In addition the spasms may be distressing to the infant and parents; if both treatments were found to be equally efficacious then it might be preferable to use the treatment that works most quickly.

Any reduction in the number of spasms suffered by non-responders would also be measured. If the duration of spasms is linked to long-term psychomotor development then likewise the number of spasms may also be important in determining long-term development. In addition if the spasms are distressing to the infant a treatment which reduces their frequency may be preferable to one that has less effect.

Relapse rates; clearly even if one treatment stopped the spasms in a greater proportion than the other, if remission of the spasms could not be maintained then if the number of patients who remained in remission in the other group was higher it might be considered to be the most efficacious treatment overall.

The precise relationship between clinical spasms and hypsarrhythmia is not clear especially with regard to long-term outcome. To be eligible for entry into the drug trial hypsarrhythmia had to be present on the entry EEG. An EEG was then to be repeated at the end of the initial two week period. It was hoped this might allow us to determine whether or not resolution of the hypsarrhythmia has any impact on the long term outcome. Patients who did not have hypsarrhythmia on the entry EEG would be asked to participate in the epidemiology trial, this would allow us to hypothesize whether patients without hypsarrhythmia at time of diagnosis have a better/worse/similar outcome to those who do have hypsarrhythmia.

It is known that in the majority of patients the natural history of the spasms is that they will resolve with time, even if the patient is untreated. Nonetheless, many patients will continue

on to develop other forms of seizures and epilepsy. It is not yet known whether controlling the spasms effectively bears any relationship to the risk of developing other seizure types. It was therefore decided that subsequent seizure types would be regarded as a long-term outcome in our group of patients and would be measured at the time of the follow up for psychomotor development. The type and frequency of seizures other than spasms suffered by the infant in the month preceding the developmental assessment at 12-14 months would be recorded.

Long term psychomotor development may be the most important outcome for this group of patients. Many would argue that any treatment proven to be most beneficial with respect to developmental progress should be used in preference to any other medication regardless of its effect on the other outcomes listed above. Developmental progress would be assessed at the time of trial entry and again at 12 -14 months of age. This would allow at least 2 months of recovery following treatment and is an age at which some language development has occurred. It is believed that delaying the assessment to a greater age will give little advantage and would have the disadvantage of increasing the impact of environmental factors. The Vineland Adaptive Behavioural Scales were chosen after lengthy consideration as the tool of choice for assessing developmental outcome in our group of patients.

The Vineland Adaptive Behaviour Scales have been developed and validated in the U.S.A. to measure "adaptive behaviour" defined as the performance of the daily activities required for personal and social sufficiency. The Vineland has four domains (communication, daily living skills, socialisation and motor skills) and these combine to give an Adaptive Behaviour Composite: each of these has a standard score of 100 with a standard deviation of 15 and each can be expressed as an age equivalent (developmental age).

One of the main benefits of the Vineland is that it can be easily adapted to be performed as a questionnaire that can be administered over the phone by a trained researcher who would be based in Bath either to the enrolling physician or parent/guardian. In addition it concentrates on the usual response, not the best response to any task. It has been validated in greater detail on larger numbers of children (3000) and has been used in the U.K. for other developmental follow-up studies. It achieves construct validity, content validity and has been compared to other scales in both normal and handicapped children. It has been shown to have internal consistency, test-retest and inter-rater reliability. It has also been designed to minimise the influence of physical handicap.

Finally side effects and deaths in each group would be recorded as these are considerations which in clinical practice often dictate the acceptability of a treatment to the clinician/patient//parent /guardian. Should an infant suffer unacceptable side effects during the trial then the treatment should be discontinued and the trial centre informed immediately. The lead clinician may then choose his own alternative treatment, but we

suggest the lead clinician change to the alternative therapy i.e. either steroids (synacthen depot or prednisolone) after vigabatrin, or vigabatrin after steroids.

Investigations

In order to understand more about the associations and aetiologies of infantile spasms we choose to collect information on the results of any investigations undertaken on any patient enrolled into the trial. As part of normal clinic practice it was anticipated that the following investigations would be undertaken on all subjects.

1. MRI or CT of the brain.
2. Urine metabolic screen for amino acids.
3. Ophthalmoscopy (either direct or indirect).
4. Ultraviolet light examination (Woods light).

We requested that the results of these tests should be forwarded to the trial centre. The following tests might also have be considered appropriate in some cases and, if performed, the results of these and any other tests would be requested.

1. Urea and electrolytes.
2. Liver function tests.
3. Chromosomes.
4. Urine metabolic screen for organic acids.
5. Lactate.
6. Biotinidase assay.
7. Ammonia.
8. Thyroid function.
9. Pyridoxine response - if pyridoxine is to be given we would recommend that pyridoxine is given one month after the start of the trial (after both the randomised treatment and first alternate treatment have been given in a child who continues fitting).

Finally, at present it is not thought that infantile spasms are genetically determined, but there are rare reports of X-linked cases in the literature[54]. To investigate the possibility of a genetic predisposition we requested that if venesection was performed for any clinical reason during the course of the infant's illness, then a blood sample be taken for DNA analysis.

Analysis

A Data Monitoring Group has been set up (appendix two) that will analyse and assess the results independently of the trial investigators (the Trial Steering Committee, appendix two) for the duration of the trial at a frequency to be recommended by the chair.

There will be post-randomisation stratification for potential confounding variables not accounted for in pre-randomisation. These include EEG appearance (i.e. hypsarrhythmia vs atypical vs normal awake, normal asleep) and diagnostic sub-groups (i.e. cerebral dysgenesis on cranial scanning, chromosomal abnormalities or other syndromes and other diagnosis such as metabolic disease). Social factors will include birth order and maternal age at school leaving.

It may be possible to see if any trends in outcome are repeated within subgroups of the trial population. The largest subgroup should be infants where development was delayed (as shown by pre-randomisation stratification data and as shown separately by the developmental history). Smaller subgroups, e.g. those diagnosed with cerebral palsy on clinical examination, cerebral dysgenesis on cranial imaging, normal awake and sleep EEGs, are unlikely to be large enough for separate analysis. However, the data will be examined in case there is a dramatic difference in outcome, or a consistent trend.

We are aware that the pattern of developmental age in the two groups may be bimodal. A direct comparison of the developmental age (total score and subsets) of the two groups will be undertaken, but we will also determine the proportion of individuals in each group whose development is one, two and three standard deviations below the mean for the Vineland.

Ethical approval was then sought and granted from the Multicentre Research Ethics Committee (MREC). Investigators are continuing to be recruited and Local Research Ethics Committees (LREC) approached. Enrolment of patients into the trial began June 1999.

REPORT ON STUDY STATUS TO THE END OF SEPTEMBER 2002

Local ethical approval had been granted in 150 centres across the UK.

Enrollment

One hundred and five infants have been enrolled into the randomised controlled drug trial and the epidemiology study.

Eighty eight infants have been enrolled into the epidemiology study only.

A further fourty four infants have been notified to the trial centre but were not eligible for inclusion into the trial.

Duration of study

Due to unforeseen delays in recruiting centres and obtaining local ethical approval, the rate of recruitment into the trial has failed to reach the above estimates. Additional funds have been granted to allow the UKISS study to continue until the end of 2002 to allow us to aim to reach an adjusted target recruitment of 125 patients into the randomised controlled drug trial, this will give us an 80% power to see a 25% difference in cessation of spasms between the two groups.

CHAPTER FIVE

The Cochrane Collaborative: a systematic review comparing the medical treatments of infantile spasms (West syndrome) in terms of long term developmental outcome, seizure control and treatment side effects.

Whilst searching the literature for information on trials and studies that had previously investigated the effect of drug treatments on IS it became clear that although there was a wealth of literature on this subject there were the following problems in trying to assess the validity, applicability and implications of the results of these studies:

1. There were few randomised controlled trials (RCTs), the majority of reports were either prospective non-randomised or retrospective studies. The main problem with non-randomised controlled trials is that they are open to selection bias: i.e. systematic differences between comparison groups in prognosis or responsiveness to treatment.
2. Many of the studies contained only small numbers of subjects with the result that they have little or no power.
3. The studies were located by traditional methods only i.e. through the electronic databases usually Medline only. The problem with this method is that only 30 – 80% of published trials can be located via any one database. In addition unpublished trials were not sought leading to publication bias: studies in which an intervention is not found to be effective are far less likely to be published thus traditional reviews tend to overestimate the true effect of an intervention.
4. Only studies published in the English language were considered, again studies in which an intervention is not found to be effective are less likely to be published in English leading to language bias.

In order to try and minimise the above problems and determine if any one treatment for IS was better in terms of long-term outcome, seizure control and side effects a systematic review in conjunction with the Cochrane Collaboration was undertaken. Although a conventional review of the literature on the treatment of IS had shown that few studies had considered the long-term outcomes (i.e. psychomotor development and progression to other seizure types) when investigating the effect of medical therapies on IS, one of the aims of this review was to set a "Gold Standard" for future studies.

It was decided that there are four important factors that must to be considered when choosing a therapy for treatment of any infant diagnosed with IS;

1. Development

   Any effect on long-term psychomotor development: arguably the most important factor.

2. Subsequent epilepsy

   Many patients continue to have other forms of epilepsy into adult life and about 20% will progress to Lennox Gastaut syndrome[113]. These patients will therefore require anticonvulsants and will continue to suffer the effects of epilepsy often for life.

Definition: Lennox Gastaut syndrome;
The Lennox-Gastaut syndrome is an age specific epileptic encephalopathy, characterised by epileptic seizures, slow spike-waves in the waking electroencephalogram (EEG) and fast rhythmic bursts during sleep, psychomotor delay and personality disorders. Its incidence is not known but it has been estimated to account for 1-10% of all childhood epilepsies. It occurs more frequently in males and onset is usually before the age of eight with a peak between three and five years

The following seizure types and EEG findings are associated with Lennox-Gastaut syndrome;

- Atypical absence seizures: these occur in the majority of cases and are frequently subtle. Loss of consciousness may be incomplete allowing the patient to continue ongoing activities. However they are often accompanied by loss of muscle tone, myoclonic jerks and drooling. EEG shows irregular diffuse slow spike-wave activity at 2 - 2.5hz.
- Tonic seizures: these are commonly seen and may be axial, appendicular or global, they may be symmetrical or unilateral. They consist of flexion of the neck and body, extension of the arms and legs and contraction of the facial muscles. There may be associated apnoea, eye rolling and facial flushing. Consciousness is usually impaired. They are usually brief, lasting seconds. The EEG shows discharges of fast bilateral bursts predominately anteriorly or on the vertex.
- Myoclonic and atonic seizures: these are less common and consist of a sudden head drop or fall to the ground and are associated with polyspikes and slow waves, or diffuse spike waves, or fast rhythms with an anterior predominance on the EEG.
- Status epilepticus and non-convulsive status occurs in approximately two thirds of patients and usually consists of continuous absence seizures punctuated by recurring tonic seizures and may be difficult to recognise.
- The waking EEG is abnormal in the vast majority of cases showing 2 to 2.5hz slow spike-wave discharges over both hemispheres with multifocal spikes and spike waves predominating in the frontal and temporal areas.

Psychomotor delay and neuropsychiatric symptoms occur in 90% of patients with Lennox-Gastaut syndrome. Language is frequently affected with both slowness in ideation and expression in addition to difficulties of motor dysfunction. Severe behavioural disorders and personality disorders are nearly always present. There is also a tendency for psychosis to develop with time. The long-term prognosis is poor; although the epilepsy often improves, complete seizure freedom is rare and conversely the mental and psychiatric disorders tend to worsen with time.[113]

3. Response: control of the spasms

   The spasms are certainly distressing for parents and may well be distressing to the infant. It is also possible that the spasms are directly linked to the development of SLD as it is generally thought by clinicians (anecdotal evidence only) that the

earlier the spasms are brought under control the better the outcome. It may of course be that those with a better prognosis have seizures that are easier to control. It was therefore decided to look at control of spasms in terms of;

- complete cessation of spasm
- time taken to achieve cessation of spasms
- reduction in total number of spasms
- relapse rates
- resolution of hypsarrhythmia

The exact relationship between clinical spasms and hypsarrhythmia on the EEG is not entirely clear. Not all infants with spasms have classical hypsarrhythmia on the EEG, and in those in whom it is present it is not always present all of the time[65]. It is not known whether presence or absence of hypsarrhythmia affects long-term outcome.

4. Side effects

These must always be taken into account. Any drug with unacceptable side effects will not be used in clinical practice. Likewise if two drugs show similar beneficial effects then the one with the safer drug profile should be used in preference.

The following review was undertaken under the aegis of the Cochrane Collaboration, it strictly adheres to the guidelines set out in the Cochrane Collaboration Handbook and was compiled and analysed using the Revman Package provided by the Cochrane collaboration.

Reviewers

Dr Eleanor Hancock (ECH), Prof. John Osborne(JPO), Prof. Phillip Milner (PLM).

Contribution of reviewers

ECH was primarily responsible for all aspects of this review including protocol design, undertaking the searches, the database of studies, data collection and extraction, data analysis and presentation of the results.

JPO and PLM agreed and approved the review at all stages and independently evaluated which studies should be included and excluded from the review and also independently extracted the data from the included studies.

Background

There have been numerous clinical trials looking at different treatment regimes in the past (discussed in detail in chapter three). The main problem is that few of the trials have been

randomised controlled trials and that the drug under investigation has frequently been used long after the onset of seizures and in addition to or after other anticonvulsants. There is wide variation in the drug dosages used and the duration for which the drugs are used. As a result it is confusing when looking at the literature to know which is the best treatment for this disorder with the consequence that many different treatment modalities are currently in use.

A conventional review of the literature on the treatment of infantile spasms carried out by Haines and Casto in 1994[81] concluded that the results of previous studies were widely varying and that well-designed, blind, prospective clinical trials are needed to answer many questions regarding the treatment of infantile spasms.

Objectives

The aim was to compare the effects of single pharmaceutical therapies used to treat infantile spasms in terms of long-term psychomotor development, subsequent epilepsy rates, control of spasms and side effects.

The following hypotheses were tested:

A. Therapy vs placebo
1. Therapy A* will give improved long term psychomotor development compared with placebo treatment.
2. Treatment of infantile spasms with therapy A* will reduce subsequent epilepsy rates compared with placebo treatment.
3. Therapy A* is more effective in controlling infantile spasms (in terms of spasm cessation, reduction in total number of spasms and relapse) than placebo treatment.
4. Therapy A* is more effective in resolving hypsarrhythmia than placebo treatment.

B. Therapy vs no treatment
1. Therapy A* will give improved long term psychomotor development compared with no treatment.
2. Treatment of infantile spasms with therapy A* will reduce subsequent epilepsy rates compared with no treatment.
3. Therapy A* is more effective in controlling infantile spasms (in terms of spasm cessation, reduction in total number of spasms and relapse) than no treatment.
4. Therapy A* is more effective in resolving hypsarrhythmia than no treatment.

C. Comparisons between therapies
1. Therapy A* will give improved long term psychomotor development compared with any other single pharmaceutical therapy.
2. Treatment of infantile spasms with therapy A* will reduce subsequent epilepsy rates compared with any other single pharmaceutical therapy.
3. Therapy A* is more effective in controlling infantile spasms (in terms of spasm cessation, reduction in total number of spasms and relapse) compared with any other single pharmaceutical therapy.
4. Therapy A* is more effective in resolving hypsarrhythmia compared with any other single pharmaceutical therapy.

*Therapy A = ACTH** or Hydrocortisone or Prednisone / Prednisolone or

Carbamazepine or Ethosuximide or Gabapentin or Lamotrigine or Phenobarbitone or Phenytoin or Topiramate or Vigabatrin or Valproate or Clonazepam or Diazepam or Nitrazepam or Pyridoxine (Vitamin B6) or any other single therapeutic agent studied in the literature.

** ACTH At the time of undertaking this review there were two "ACTH" preparations in widespread use; ACTH (adrenocorticotrophin hormone) and tetracosactrin. ACTH is a natural product derived from a bovine source administered as a daily intramuscular injection. However, in the UK, with the existing concerns surrounding bovine spongiform encephalopathy (BSE) ACTH has been withdrawn from the market.

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of the administration of drug therapy to infants and children with infantile spasms were included in this review, including trials which compared a therapy with none or placebo and trials that compared one drug with another.

Definition of RCT: trials in which participants are prospectively allocated to treatment groups by a random (e.g. random number generation, coin flips) or quasi random (e.g. by date of birth) process.

If the study was not an RCT it was not included in the review: the existence of such studies was documented.

We considered studies looking at drug therapy as second line therapy as well as those studies looking at drug therapies as first line therapy.

Types of participants

Any infant or child treated for infantile spasms, regardless of whether or not EEGs were performed or whether therapy had been given prior to trial entry.

As the majority of published studies on infantile spasms did not give a definition of infantile spasms used for their participants, for the purpose of this review, we assumed a clinical diagnosis had been made for any participant that was entered into a trial. We documented any definitions which were given, and considered whether differences in definition might account for between study variation.

Types of interventions

1. Any trial that compared at least one therapy against placebo treatment
2. Any trial that compared at least one therapy against no therapy
3. Any trial that compared at least one therapy against another therapy

Therapies included:

1. "Steroids"; ACTH, Tetracosactrin, Hydrocortisone, Prednisone/prednisolone.
2. Antiepileptic drugs; Carbamazepine, Clonazepam, Diazepam, Ethosuximide, Gabapentin, Lamotrigine, Nitrazepam, Phenobarbitone, Phenytoin, Pyridoxine, Sodium Valproate, Topiramate, Vigabatrin.
3. Methysergide and methylparatyrosine.
4. Any other single therapeutic agent studied in the literature.

Any dose regime of the above therapies was included.

Types of outcome measures

1. Long term psychomotor development

This was to be analysed in months as a measure of the deviation from the chronological age. It was to be measured at 3 months post entry into the trial and where possible at 5 years of age. It was measured as a continuous variable.

2. Subsequent epilepsy rates

The diagnosis of any other epileptic seizure type other than infantile spasms after the commencement of therapy constituted subsequent epilepsy. It was to be measured at three months post entry into the trial and where possible at five years of age. Any seizure type plus each seizure type (e.g. primary generalised, partial etc.) was to be measured as a dichotomous variable (i.e. present / absent) over the previous one month at three months post entry and over the previous six months at five years of age.

Because of the difficulty of defining epileptic seizures in children we would use the original authors' diagnosis.

3. Cessation of spasms

This was defined as total cessation of spasms for at least 48 hours after commencing therapy, but occurring within a month of commencement of therapy. It was measured as a dichotomous variable (i.e. ceased / continuing). Time taken from commencement of therapy to cessation of spasms was also to be measured as a continuous variable (measured

in days).

4. Quantitative reduction of spasms

This was measured as the number of spasms occurring before treatment was commenced compared with the number occurring following treatment and was to be measured as a dichotomous variable (i.e. greater than 50% reduction or less than 50% reduction in the number of spasms occurring / day over the seven day period before trial entry and over a seven day period at one month of commencing therapy).

5. Relapse rates of spasms

A single spasm occurring by one year of age or within the study period, but after cessation of spasms constituted a relapse. It was measured as a dichotomous variable (i.e. relapse occurred / no relapse occurred). Time taken from cessation of spasms to relapse was also to be measured as a continuous variable (measured in days) in those patients in whom spasms had ceased.

6. Resolution of hypsarrhythmia

Patients were divided into those who had a normal EEG prior to entry into a study and those who did not. In the group that did not have a normal EEG on entry, the EEG appearance after treatment was divided into those in whom the EEG remained abnormal and those in whom it became normal. It was measured as a dichotomous variable (i.e. normal / abnormal).

7. Side effects

Only side effects that were considered severe enough to warrant discontinuation of the test treatment were measured. They were measured as a dichotomous variable i.e. therapy stopped vs therapy not stopped. They were also qualitatively summarised.

8. Deaths

All deaths were measured. They were measured as a dichotomous variable (i.e. alive / deceased).

Search strategy for identification of studies

In addition to searching the central trials register of the Cochrane Epilepsy Group (see group module) we searched:

1. MEDLINE Database (1960 to 2001) according to the search strategy used by the Cochrane Epilepsy Group.

2. EMBASE Database (1981 to 2001).

3. The reference lists of both the Randomised Controlled Trials and rejected articles were

scanned (by ECH) to identify possible articles missed by the computerised search.

4. Correspondence with colleagues to try and identify unpublished data. Correspondence with authors of review articles has not yet been undertaken.

5. Correspondence with drug companies to try and identify unpublished data.

6. Appeals at international conferences to delegates to try and identify unpublished data and studies not published in English.

Methods of the review

Relevant publications were reviewed independently by the three reviewers (Dr Hancock, Professor Osborne and Professor Milner). Discrepancies were resolved by discussion. There was no blinding of authorship or results. All randomised controlled trials were considered. All non-English studies were also considered.

1. Exclusion criteria

- Any trial that was not a RCT was excluded from analysis but was documented.
- If a clinical definition for infantile spasms was given; in any trial in which there was doubt about the clinical diagnosis, the trial was excluded from analysis, but was documented.

2. Assessment of methodological quality

- Selection bias: the studies were assessed as to whether allocation concealment was adequate, unclear or inadequate.
- Performance bias: The studies were assessed as to whether recipients and those measuring outcome were unaware of the assigned therapy (However we accepted that the majority of the studies in this review would not be double blinded trials)
- Attrition bias was assessed as to whether there was loss of patients to follow up.

Using the above criteria studies were then divided into (1) those with a low risk of bias (2) those with a moderate risk of bias and (3) those with a high risk of bias. (See Cochrane Handbook section 6.7.1)

In studies where it was unclear if the above criteria have been met then the reviewers are endeavouring to obtain additional information by contacting the first author on up to three occasions. This will be documented.

The following data was extracted independently by the three reviewers (Dr Hancock, Professor Osborne and Professor Milner) and discrepancies resolved by discussion.

1. Participants (i.e. those characteristics of the population that may affect outcome regardless of treatment):

· age at spasm onset, diagnosis and start of treatment (mean, median and range measured to the nearest completed week of age).

· time taken from onset of spasms to initiation of treatment (mean, median and range measured to the nearest completed week).

· sex (male, female).

· previous treatment (e.g. prednisolone, ACTH, vigabatrin, valproate).

2. Interventions:

· type of pharmaceutical agent used (e.g. prednisolone, ACTH, vigabatrin, valproate).

· dose (measured in the internationally accepted units i.e. mg for prednisolone, IU for ACTH).

· frequency (measured as the number of times the pharmaceutical agent is given in a 24 hour

period).

· route of administration (i.e. oral, intramuscularly, intravenously).

· treatment length (measured to the nearest completed day).

3. Outcome measures:

· psychomotor development.

· subsequent epilepsy rates.

· cessation of spasms and the time taken to cessation of spasms.

· reduction in spasms.

· relapse rates and the time taken to relapse.

· resolution of hypsarrhythmia and the time until resolution.

· side effects.

· deaths.

Analysis plan

1. Study quality; this was done by a table of met / unmet criteria for selection, performance and attrition bias.

2. Dichotomous data; for each item of data requiring dichotomous analysis the following

was recorded; no. of patients who experienced the event (or outcome) in each group for each comparison and the total number in each group. They were analysed using Peto odds ratios in the Cochrane RevMan Package.

3. Continuous data: for each item of data requiring continuous data analysis, except psychomotor development the following were recorded; number of patients in each group, the mean value for the outcome in each group and the standard deviation. They were analysed using weighted means in the Cochrane RevMan Package

4. When data for the same outcome is presented in some studies as dichotomous and in others as continuous data then we are endeavouring to obtain continuous data from the investigators. If it is not possible to obtain continuous data, for example because it was not recorded then the data will either be analysed as dichotomous data with a "cut off" point agreed by the three reviewers or a mixture of dichotomous and continuous data will be analysed using two separate tables.

5. We looked for sources of heterogeneity between trials of methodological and clinical differences, including previous treatment for spasms, age at trial entry, single underlying cause. We also looked for subgroup analysis of clinical features, for example; developmental delay prior to onset of spasms, differences in drug dosages, timing and length of treatment and specific underlying diagnosis such as tuberous sclerosis.

Description of studies

The literature search of the central trials register of the Cochrane Epilepsy Group found 13 potential studies. The literature search of MEDLINE (1960-2001) found 33 potential studies, and the literature search of EMBASE (1981-2001) found 14 potential studies. Some studies were identified from more than one database. From these three databases a total of 43 potential studies were identified. The references of these 43 studies were then scanned by Dr Hancock and a further 9 possible studies identified. Direct correspondence with colleagues and appeals at international conferences (Seattle September 2000 and Tokyo February 2001) also identified two of the above (Appleton 1999 and Vigevano 1997 pre-publication) randomised controlled trials (and two ongoing trials). Correspondence with drug companies did not identify any further trials. This brought the total to 52 studies to be evaluated for inclusion into this review (see appendix three for references). We intend to continue correspondence with authors, colleagues and drug companies and to regularly update our literature searches of the above databases, so that we may update this review as future studies are completed. Hand searching of journals has not yet been

possible.

Table fourteen

Study	Methods	Participants	Interventions	Outcomes
Appleton 1999[1]	Randomised controlled trial	40 patients with a clinical definition of infantile spasms and hypsarrhythmia on EEG.	Vigabatrin Placebo	Cessation of spasms Reduction in spasms Relapse rate Resolution of EEG
Baram 1996[2]	Randomised controlled trial	29 patients with a diagnosis confirmed on video EEG	ACTH Prednisone	Cessation of Spasms Relapse rates Resolution of EEG
Chiron 1997[3]	Randomised controlled trial	22 patients with a clinical diagnosis of infantile spasms or hypsarrhythmia on EEG	Vigabatrin Hydrocortisone	Cessation of spasms Relapse rates Resolution of EEG
Dreifuss 1986[4]	Randomised controlled trial	52 patients with a diagnosis of hypsarrhythmia on EEG	ACTH Nitrazepam	Reduction in seizures
Dyken 1985[5]	Randomised controlled trial	17 patients with a clinical definition of infantile spasms and hypsarrhythmia on EEG.	Valproate Placebo	Reduction in spasms
Hrachovy 1983[6]	Randomised controlled trial	24 patients with a clinical definition of infantile spasms and hypsarrhythmia on EEG.	ACTH Prednisone	Cessation of spasms
Hrachovy 1989[7]	Randomised controlled trial	24 patients with a clinical definition of infantile spasms and hypsarrhythmia on EEG.	Methysergide Alpha-methylparatyrosine	Cessation of spasms Reduction in spasms
Hrachovy 1994[8]	Randomised controlled trial	59 patients with a clinical definition of infantile spasms and hypsarrhythmia on EEG.	ACTH high dose ACTH low dose	Cessation of spasms Relapse rates Resolution of EEG
Vigevano 1997[9]	Randomised controlled trial	42 patients with a diagnosis according to the ILAE classification	Vigabatrin ACTH	Cessation of spasms Relapse rates Subsequent epilepsy rates Resolution of Hypsarrhythmia
Yanagaki 1999[10]	Randomised controlled trial	26 patients with a diagnosis confirmed on video EEG	ACTH high dose ACTH low dose	Cessation of spasms Relapse rates Resolution of hypsarrhythmia Developmental outcome

Table showing the characteristics of included studies

Review of the studies eliminated 36[11-46] studies because they were not randomised controlled trials, a further four[47-50] because the subjects did not suffer from infantile spasms and one paper[51] was excluded because the data referred to the effects of hormonal treatment on the brain when imaged using computerised tomography, it did not report any

other outcome measure. This left a total of eleven papers[1-10 52], in one of these; Vigevano 1994[52] all the data was included in a further paper Vigevano 1997. This gave a total of ten randomised controlled trials[1-10] looking at the treatment of infantile spasms, with a total of 335 patients. These ten studies looked at eight different pharmacological agents for the treatment of infantile spasms; vigabatrin, ACTH (including six different treatment regimes), prednisone, hydrocortisone, nitrazepam, sodium valproate, methysergide and alpha-methylparatyrosine (see table fourteen).

- **Appleton 1999[1]**

This was a short term randomised, double-blind, placebo-controlled multicentre trial of 40 patients. Inclusion criteria included patients aged between 1 and 20 months with newly diagnosed and previously untreated infantile spasms in whom the EEG demonstrated either classical or modified hypsarrhythmia. A spasm was defined as a sudden, generally bilateral and symmetric contraction of the muscles of the neck, trunk and extremities (flexor, extensor or mixed). The principal exclusion criteria was the use of any medication, including steroids, that could be considered to be an antiepileptic drug within a 2-month period before entry into the trail. The trial consisted of a 5-day double-blind phase during which patients received either vigabatrin or placebo. Twenty patients received vigabatrin and twenty placebo. The initial starting dose was 50 mg/kg/day for 24 hours, if spasms did not cease completely, the dose was increased to 100/mg/kg/day and maintained for a further 48 hours. The dose could then be increased further to 150/mg/day. Randomisation was pre-determined by a code held by the pharmacy department of each participating hospital. Both the recipients and assessors were blinded. Outcomes reported were cessation of spasms, reduction in spasms, resolution of hypsarrhythmia and relapse rates. Some patients were lost to follow up, but not during the double-blind phase.

- **Baram 1996[2]**

This was a randomised single-blinded single-centred trial of 29 patients. Infants with clinical infantile spasms were considered for the study and underwent 24-hour video-EEG to ascertain hypsarrhythmia and clinical spasms. The trial consisted of a two week period during which 15 patients were treated with ACTH, 150 units/m.squared/day, intramuscularly in two divided doses and 14 patients treated with prednisone 2 mg/kg/day given orally in two divided doses. A computer-generated random-number list determined treatment, and concealment of allocation was not clearly stated, but has been confirmed by Dr Baram (direct correspondence). Blinding of recipients was not done, but blinded assessment of outcomes was performed. Outcomes reported were, subsequent seizure rates (short term only), cessation of spasms, resolution of hypsarrhythmia, relapse rates and development of other seizure types within the follow-up period.

- **Chiron 1997[3]**

This was a randomised multicentre trial of 22 patients with infantile spasms all of whom had tuberous sclerosis. Inclusion criteria included epileptic spasms recorded on EEG or seen by an experienced clinician, diffuse interictal paroxysmal activity and age ranging from 1 month to 2 years. Patients were excluded if they had been previously treated with steroids or vigabatrin, but not other anticonvulsant medications. The trial consisted of a one month period during which 11 infants received vigabatrin at a dose of 150 mg/kg/day and 11 infants received hydrocortisone at a dose of 15 mg/kg/day. The method of

randomisation was not stated. Neither recipients nor assessors were blinded. Outcomes reported were cessation of spasms, resolution of hypsarrhythmia and relapse rates.

- **Dreifuss 1986**[4]

This was a randomised multicentre trial of 52 patients. Inclusion criteria included patients aged between 1 and 24 months of age with infantile spasms documented by a hypsarrhythmic or modified hypsarrhythmic pattern on EEG. None of the patients had received steroids or nitrazepam prior to entry into the trial. The trial consisted of a four week period during which 27 patients received nitrazepam and 25 patients ACTH. Nitrazepam was started at 0.2 mg/kg/day in two divided doses or 1 mg twice daily, whichever was greater and was adjusted twice weekly by increments of 0.3 to 0.4 mg/kg/day. Maintenance dosage ranged from 4.8 to 9 mg/day. ACTH was given as a once daily intramuscular injection of 40 units. A computer-generated randomisation code determined treatment, but concealment of allocation was not clearly stated. Blinding of recipients was not done, but blinded assessment of outcome was performed. The only outcome reported was reduction in spasm frequency. There was a discrepancy between the reviewers over the assessment of how many patients were lost to follow up in this trial, this discrepancy arose because the authors are unclear in their paper as to how many patients were lost to follow up. We are intending to contact the author in order to clarify this point so that it may be included in a future update of the review, in the meantime it remains unclear as to the number of patients lost to follow up.

- **Dyken 1985**[5]

This was a randomised, placebo-controlled-cross-over single-centre trial of 17 patients. Inclusion criteria included patients aged between 8 and 83 months of age with a clinical diagnosis of infantile spasms and hypsarrhythmia on EEG, who had previously failed to respond to steroids. Many patients had received other anticonvulsant medication. The trial compared sodium valproate against placebo but the length of the trial and dosages used were not given. A computer-generated random numbers table was used to allocate patients, but concealment of allocation was not clearly stated. Blinding of recipients and blinded assessment of outcome were performed. They only reported reduction in spasm frequency as an outcome. Four patients were lost to follow up.

- **Hrachovy 1983**[6]

This was a randomised single-centre trial (using a double-dummy technique) of 24 patients. Inclusion criteria included patients with infantile spasms and hypsarrhythmic EEG patterns on serial 24-hour video and polygraphic monitoring. No patient had been previously treated with steroids, but some had received other anticonvulsant medications. Twelve patients received ACTH 20 - 30 units/day for two weeks, which was then tapered over one week if a response was seen. If a response was not seen, they received a further four weeks before the dose was tapered. These patients also received a prednisone placebo. Twelve patients received prednisone, 2 mg/kg/day for two weeks, which was then tapered over one week if a response was seen. If a response was not seen, they received a further four weeks before the dose was tapered. These patients also received an ACTH gel placebo. The method of randomisation was not given. Blinding of recipients was done but it was unclear if blinded assessment of outcome was performed. Outcomes reported were complete cessation of spasms and relapse rates.

- **Hrachovy 1989**[7]

This was a randomised trial of 24 patients. Inclusion criteria included newly diagnosed patients with infantile spasms and hypsarrhythmic EEGs. The trial consisted of a three week period during which, twelve patients were treated with methysergide, 2 mg/m.squared/day for the first seven days, then 5 mg/m.squared/day for the next 14 days and twelve patients were treated with alpha-methylparatyrosine 500 mg/m.squared/day, increasing by 150 mg/m.squared/day on day two and thereafter until a maximum dosage of 1,250 mg/m.squared/day was reached. The method of randomisation was not given. It was not clear that recipients and assessors were blinded. They reported cessation of spasms, a reduction in the number of spasms (and developmental status at 3 weeks) as outcome measures.

- **Hrachovy 1994**[8]

This was a randomised controlled trial of 59 patients. Inclusion criteria included infants in whom a diagnosis of infantile spasms had recently been made, who had hypsarrhythmic EEG findings. They were excluded if they had previously received steroids. Thirty patients received 150 units/m.squared of ACTH per day for three weeks with a tapering dose over a further nine weeks, and twenty-nine patients received 20-30 units/day of ACTH for two to six weeks, tapering over one week. The method of randomisation was not stated. Blinding of recipients was not done, but blinded assessment of outcomes was performed. Outcomes reported were complete cessation of spasms, resolution of hypsarrhythmia and relapse rates. They had loss of follow up of nine patients.

- **Vigevano 1997**[9]

This was a randomised (response mediated, cross-over) single-centre trial of 42 patients. Inclusion criteria included patients with newly diagnosed and previously untreated infantile spasms diagnosed according to the ILAE classification. Twenty three patients received vigabatrin at 100-150 mg/kg/day and nineteen received ACTH at 10 units/day. The method of randomisation was not stated. Blinding of recipients was not done and it was not clear if the assessors of outcome were blinded. Outcomes reported were cessation of spasms, resolution of hypsarrhythmia, (and short term effects on subsequent epilepsy rates and cognitive function).

- **Yanagaki 1999**[10]

This was a randomised single-centre trial of 26 patients. Inclusion criteria included patients with infantile spasms and hypsarrhythmia on video EEG. Patients were excluded if they had received previous steroid or intravenous gamma globulin treatment. Thirteen patients received 1 unit/kg/day of synthetic ACTH for two weeks tapering over a further two weeks and thirteen patients received 0.2 units/kg/day of synthetic ACTH for two weeks tapering over a further two weeks. The method of randomisation was not stated. It was not clear whether recipients and assessors were blinded. Outcomes reported were cessation of spasms, resolution of hypsarrhythmia, relapse rates (and the short term effect on development). One patient was lost to follow up.

Methodological quality of included studies

Overall, methodological quality of the included studies was poor. All the studies had small numbers of participants, the largest having only 59 patients[8] (although results were only given for 50 of these patients), subsequently the power of each individual study was low.

There were only two placebo-controlled trials[1 5] (one further trial used a double dummy technique[6]). Although all the studies stated that they were randomised controlled trials, only four gave the method of randomisation, and only two stated that concealment of allocation had been performed. Blinding of recipients occurred in only three studies, did not take place in five studies and was unclear in the remaining studies. Six studies clearly stated that those measuring outcome were unaware of the assigned therapy. At least four studies had loss of patients to follow up. Three of the studies were multicentre trials, four studies recruited patients from a single centre and it was unclear in the remaining three studies how many centres were involved in recruiting patients. Of the ten RCTs considered in this review, all but one had a high risk of bias (see table fifteen).

Table fifteen

Study ID	Number of patients	Placebo RCT	Allocation blinded	Recipients blinded	Outcome blinded	Loss to follow up	Risk of bias
Appleton 1999[1]	40	Yes	Yes	Yes	yes	No	Low
Baram 1996[2]	29	No	Yes	no	yes	no	moderate
Chiron 1997[3]	22	No	not clear	No	No	no	High
Dreifuss 1986[4]	52	No	not clear	no	yes	yes	high
Dyken 1985[5]	17	Yes	not clear	yes	yes	yes	high
Hrachovy 1983[6]	24	Yes	not clear	yes	yes	no	high
Hrachovy 1989[7]	24	No	not clear	Not clear	Not clear	no	high
Hrachovy 1994[8]	59	No	not clear	No	yes	yes	high
Vigevano 1997[9]	42	No	not clear	No	Not clear	No	high
Yanagaki 1999[10]	26	No	not clear	Not clear	Not clear	yes	high

Table showing methodological quality of included studies

Results

Participants, those characteristics of the population that may affect outcome regardless of treatment (see table sixteen).

The male: female ratio was given for six of the studies and was 1:1.

The age at spasm onset was given in four studies and ranged from 20 to 30 weeks.

The age at which diagnosis of spasms was made was not given in any study.

The age at trial entry (i.e. the age at which the trial treatment was started) was given in six studies and ranged from 22 to 41 weeks.

The time delay between onset of spasms and start of treatment was given in three studies and ranged from 3 to 16 weeks.

In two studies other treatments had been previously tried, in two studies other treatments had not been used, and in six studies it was unclear.

We had also planned to look for heterogeneity according to different diagnostic groupings for example tuberous sclerosis and Down's syndrome and also looking at whether patients had developmental delay prior to the onset of spasms. Unfortunately, for the majority of the studies this information was not available and could not, therefore be analysed.

Table sixteen

Study ID	Intervention	Male:Female	Age at onset	Age at diagnosis	Age at trial entry	Delay to treatment	Previous treatment
Appleton 1999[1]	Vigabatrin	11:9	30 weeks	Not available	35 weeks	6 weeks	No
	Placebo	8:12	26 weeks	Not available	35 weeks	7 weeks	No
Baram 1996[2]	ACTH	4:11	Not available	Not available	22 weeks	Not available	Not available
	Prednisone	8:6	Not available	Not available	32 weeks	Not available	Not available
Chiron 1997[3]	Vigabatrin	5:6	25 weeks	Not available	29 weeks	3 weeks	Not available
	Hydrocortisone	5:6	26 weeks	Not available	34 weeks	8 weeks	Not available
Driefuss 1986[4]	Nitrazepam	14:13	Not available	Not available	37 weeks	Not available	Not available
	ACTH	15:10	Not available	Not available	35 weeks	Not available	Not available
Dyken 1985[5]	Valproate	Not available	Not available	Not available	Not available	Not available	Yes
	Placebo	Not available	Not available	Not available	Not available	Not available	Yes
Hrachovy 1983[6]	ACTH	Not available	Not available	Not available	Not available	Not available	Not available
	Prednisone	Not available	Not available	Not available	Not available	Not available	Not available
Hrachovy 1989[7]	Methysergide	Not available	Not available	Not available	Not available	Not available	Not available
	Methylparatyrosine	Not available	Not available	Not available	Not available	Not available	Not available
Hrachovy 1994[8]	ACTH (high-dose)	Not available	Not available	Not available	Not available	Not available	Not available
	ACTH (low-dose)	Not available	Not available	Not available	Not available	Not available	Not available
Vigevano 1997[9]	Vigabatrin	14:9	25 weeks	Not available	27 weeks	Not available	No
	ACTH	7:12	26 weeks	Not available	Not available	Not available	No
Yanagaki 1999[10]	ACTH (high-dose)	8:5	20 weeks	Not available	28 weeks	7 weeks	yes
	ACTH (low-dose)	7:5	23 weeks	Not available	41 weeks	16 weeks	yes

Table showing the characteristics of the population that may affect outcome regardless of treatment

VIGABATRIN VERSUS PLACEBO

There was one study Appleton 1999[1].

- Effects on psychomotor development was not reported as an outcome in this study.
- Effects on subsequent seizure rates was not reported as an outcome in this study.
- Effects on cessation of spasms: Appleton 1999 had 40 patients and showed complete cessation of spasms in seven of twenty (35%) of patients treated with vigabatrin compared with two of twenty (10%) treated with placebo, Peto odds ratio 4.1 (95% CI 0.9 to 17.5).
- Effects on time taken to achieve cessation of spasms was not reported as an outcome in this study.
- Effects on reduction in the number of spasms: Appleton 1999 showed an >70% reduction in spasms in 40% of the group treated with vigabatrin compared with 15% in the group treated with placebo. However, it is not clear from the paper to what proportion of the two groups of patients these figures apply, whether the figures apply to the whole group or just those patients in whom complete cessation of spasms was not achieved.
- Effects on relapse rates: Appleton 1999, four out of seven patients who responded to vigabatrin relapsed and all the patients successfully treated with placebo relapsed.
- Overall only three patients treated with vigabatrin and no patient treated with placebo treatment remained spasm free within the four week study period, Peto odds ratio 8.2 (95% CI 0.8 to 84).
- Effects on time taken to relapse was not reported as an outcome in this study.
- Effects on resolution of hypsarrhythmia: Appleton 1999, five of the seven patients who were spasm free with vigabatrin showed resolution of hypsarrhythmia on EEG, compared with one of the two patients who had become spasm free on placebo, Peto odds ratio 2.4 (95% CI 0.1 to 54.6).
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in this study.
- No side effects severe enough to warrant stopping treatment were reported in this study.
- No deaths were reported.

SODIUM VALPROATE VERSUS PLACEBO

There was one study Dyken 1985[5]

- Effects on psychomotor development was not reported as an outcome in this study.
- Effects on subsequent seizure rates was not reported as an outcome in this study.
- Effects on cessation of spasms was not reported as an outcome in this study.
- Effects on time taken to achieve cessation of spasms was not reported as an outcome in this study.
- Effects on reduction in the number of spasms: Dyken 1985 used a spasm index: S.I. = (spasm frequency x spasm duration / total observation time) x 1000 to calculate the mean reduction in spasm frequency from the baseline. At the end of the four week treatment period, the valproate treatment was found to have a lower mean spasm index than placebo, when valproate was administered first ($p<0.04$). There was no significant difference between placebo and valproate during the second level of treatment. It is not possible to calculate a Peto odds ratio.
- Effects on relapse rates was not reported as an outcome in this study.
- Effects on time taken to relapse was not reported as an outcome in this study.
- Effects on resolution of hypsarrhythmia was not reported as an outcome in this study.
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in this study.
- Side effects were not reported as an outcome in this study.
- Deaths were not reported as an outcome in this study.

VIGABATRIN VERSUS HYDROCORTISONE

There was one study Chiron 1997[3]

- Effects on psychomotor development was not reported as an outcome in this study.
- Effects on subsequent seizure rates was not reported as an outcome in this study.
- Effects on cessation of spasms: Chiron 1997 comparing vigabatrin (150 mg/kg/day) and hydrocortisone (15 mg/kg/day) in twenty-two infants with infantile spasms due to tuberous sclerosis, found in the initial phase, eleven of the eleven patients (100%) treated with vigabatrin to be spasm free as compared to five of eleven patients (45%) treated with hydrocortisone. Peto odds ratio 13.8 (95% CI 2.21 to 86.35).

- Effects on time taken to achieve cessation of spasms: Chiron 1997; on average the 11 responders to vigabatrin took 4 days (range 0.5-14 days, median 2 days) to achieve complete cessation of spasms, whilst the 5 responders to hydrocortisone took an average of 13 days (range 3-30 days, median 23.5 days), WMD = -8.8 (-19.2 to 1.6).
- Effects on reduction in the number of spasms was not reported as an outcome in this study.
- Effects on relapse rates: Chiron 1997, ten of the eleven patients who responded to vigabatrin remained spasm free, this information was not given for the five responders to hydrocortisone.
- Effects on time taken to relapse was not reported as an outcome in this study.
- Effects on resolution of hypsarrhythmia was not reported as an outcome in this study.
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in this study.
- Side effects: Chiron 1997 reported that hydrocortisone had to be stopped in one patient, no reason was given.
- No deaths were reported in this study.

VIGABATRIN VERSUS ACTH

There was one study Vigevano 1997[9]

- Effects on psychomotor development: Vigevano 1997 stated that there was no apparent difference in cognitive development between the two groups during follow up which ranged from 9 to 44 months. They did not state how they assessed development or quantify it any further, and this comparison was confounded by the fact that some infants initially randomised to receive vigabatrin went on to receive ACTH, and vice versa, within the follow up period. They did not consider long-term developmental status at 5 years of age.
- Effects on subsequent seizure rates: Vigevano 1997 found an incidence of other types of epileptic seizures to be 25% in both groups during follow up of 9 to 44 months. Again they did not consider subsequent epilepsy rates at 5 years of age. Again, this comparison was confounded by the fact that some infants initially randomised to receive vigabatrin went on to receive ACTH, and vice versa, within the follow up period.

- Effects on cessation of spasms: Vigevano's 1997 trial of forty-two patients showed cessation of spasms in eleven of the twenty-three patients randomised to vigabatrin compared with fourteen of the nineteen patients randomised to ACTH. Peto odds ratio 0.4 (95% CI 0.1 to 1.2)
- Effects on time taken to achieve cessation of spasms: Vigevano 1997, the 11 responders to vigabatrin took between 1 and 14 days to achieve complete cessation of spasms, whilst the 14 responders to ACTH took between 2 and 12 days.
- Effects on reduction in the number of spasms was not reported as an outcome in this study.
- Effects on relapse rates was not reported as an outcome in this study.
- Effects on time taken to relapse was not reported as an outcome in this study.
- Effects on resolution of hypsarrhythmia: Vigevano 1997, resolution occurred in four out of eleven patients responding to vigabatrin and eleven out fourteen patients responding to ACTH. Peto odds ratio 0.2 (95% CI 0.0 to 0.9).
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in this study.
- Side effects: Vigevano 1997 stopped vigabatrin in one patient because of excessive irritability and ACTH in one patient, no reason given.
- Deaths: One patient in Vigevano's 1997 study died, but the cause was not given and it is unclear to which treatment group they had been randomised.

ACTH VERSUS PREDNISONE

There were two studies Baram 1996[2] and Hrachovy 1983[6]. The doses of ACTH used in these two studies differed, so the results should be interpreted with caution.

- Effects on psychomotor development was not reported as an outcome in these studies.
- Effects on subsequent seizure rates: Baram 1996 in their study comparing ACTH with prednisone found seven (~50%) patients in both groups to have developed other seizure types over the period of follow up of 2 to 48 months. However, this comparison was confounded by the fact that some infants initially randomised to receive prednisone went on to receive ACTH within the follow up period. They did not report subsequent epilepsy rates at 5 years of age.
- Effects on cessation of spasms: Baram 1996 compared fifteen patients treated with ACTH (150 units/m.squared/day) with fourteen treated with prednisone (2

mg/kg/day). and showed ACTH to be superior to prednisone with cessation of spasms in thirteen of fifteen (87%) patients and four of fourteen (29%) patients respectively. Hrachovy 1983 compared twelve patients treated with ACTH (20 -30 units/day) with twelve patients treated with prednisone (2 mg/kg/day). In the initial phase of the trial five of twelve (42%) patients treated with ACTH had complete cessation of spasms and resolution of hypsarrhythmia on their EEG compared with four of twelve (33%) treated with prednisone. Combining the two studies, ACTH stopped the spasms in 67.5% of patients compared with prednisone in 31% of patients, Peto odds ratio 4.2 (95% CI 1.4 to 12.4).

- Effects on time taken to achieve cessation: Baram 1996; on average the 13 responders to ACTH took 3.2 days (range 1-7 days, median 2 days) to achieve complete cessation of spasms, whilst the 4 responders to prednisone took an average of 4 days (range 2-7 days, median 3.5 days), WMD = -0.8 (95% CI -3.3 to 1.7).
- Effects on reduction in the number of spasms was not reported as an outcome in these studies.
- Effects on relapse rates: Baram 1996, two of the thirteen patients who responded to ACTH relapsed and none of the four responders to prednisone relapsed. Hrachovy 1983, three of the five patients who responded to ACTH relapsed and one of the four responders to prednisone also relapsed.
- Overall, Baram 1996, eleven patients who responded to ACTH remained spasm free and the four responders to prednisone also remained spasm free. Hrachovy 1983, two patients successfully treated with ACTH remained spasm free and three successfully treated with prednisone remained spasm free within the study period. The combined Peto odds ratio for these two studies is 2.6 (95% CI 0.8 to 8.1).
- Effects on time taken to relapse was not reported as an outcome in these studies.
- Effects on resolution of hypsarrhythmia: Baram 1996, this study showed ACTH to be superior to prednisone with resolution of hypsarrhythmia in thirteen of fifteen patients treated with ACTH compared to four of fourteen of patients treated with prednisone, Peto odds ratio 10.1 (95% CI 2.4 to 43.2). Hrachovy 1983, five of twelve patients treated with ACTH had resolution of hypsarrhythmia but this was not reported for the group treated with prednisone.
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in these studies.

- Side effects were not reported as an outcome in these studies.
- No deaths were reported in these studies.

HIGH DOSE ACTH VERSUS LOW DOSE ACTH

- There were two studies Hrachovy 1994[8] and Yanagaki 1999[10]. Hrachovy used natural ACTH and Yanagaki used synthetic ACTH. This makes direct comparison difficult. Yanagaki states that the dose equivalent of 1 IU of natural ACTH is 0.025 IU of synthetic ACTH, but the results must be interpreted with caution.
- Effects on psychomotor development: Yanagaki 1999 in their study comparing high-dose ACTH with low-dose ACTH used the Japanese Tsumori scale to evaluate developmental status at entry into the trial and in 17 responders who were followed up for more than one year. They found no significant difference in developmental quotient between the two groups at the end of the follow up period. However, they only considered psychomotor development in the responders which gives rise to biased analysis and this should be interpreted with caution. They did not consider long-term developmental status at 5 years of age.
- Effects on subsequent seizure rates was not reported as an outcome in these studies.
- Effects on cessation of spasms: Hrachovy 1994 randomised thirty patients to high-dose ACTH (150 units/m.squared/day for three weeks with a tapering dose over a further nine weeks), and twenty-nine patients to low-dose ACTH (20-30 units/day for two to six weeks, tapering over one week). Of the thirty patients treated with high dose therapy thirteen (50%) had complete cessation of spasms and of the twenty-nine patients treated with low dose therapy fourteen (58%) had complete cessation of spasms. Yanagaki 1999 randomised thirteen patients to receive 1 unit /kg/day (equivalent to 40 units/ kg/ day of natural ACTH) for two weeks tapering over a further two weeks and thirteen patients to receive 0.2 units/kg/day (equivalent to 8 units/kg/day of natural ACTH) for two weeks tapering over a further two weeks. Of the patients treated with high-dose ACTH, spasm cessation occurred in eleven of thirteen patients compared with nine of thirteen treated with low dose ACTH. Combining these two studies, "high-dose" ACTH stopped the spasms in 79.5% patients compared with "low-dose" ACTH in 76.5% of patients, Peto odds ratio 1.1 (95% CI 0.4 to 2.6).
- Effects on time taken to achieve cessation of spasms was not reported as an outcome in these studies.

- Effects on reduction in the number of spasms was not considered as an outcome in these studies.
- Effects on relapse rates: Hrachovy 1994, two of the thirteen patients who responded to "high-dose ACTH" relapsed and two of the fourteen patients who responded to "low-dose ACTH" also relapsed. Yanagaki 1999, three of the eleven patients who responded to "high-dose ACTH" relapsed and three of the nine responders to "low-dose ACTH" relapsed.
- Hrachovy 1994, eleven patients who responded to high-dose ACTH remained spasm free and twelve patients who responded to low-dose ACTH also remained spasm free. Yanagaki 1999, eight patients who responded to high-dose ACTH remained spasm free and six patients who responded to low-dose ACTH remained spasm free. Combining these two studies gives a Peto odds ratio 0.8 (95% CI 0.3 to 1.9).
- Effects on time taken to relapse was not considered as an outcome reported in these studies.
- Effects on resolution of hypsarrhythmia: Hrachovy 1994, three out of thirteen responders to high-dose ACTH showed resolution of their EEG and three out of fourteen responders to low-dose ACTH showed resolution of their EEG. Yanagaki 1999, eight out of thirteen treated with high-dose ACTH showed resolution of their EEG and seven out of twelve treated with low-dose ACTH showed resolution of their EEG. Combining these two studies gives a Peto odds ratio 1.9 (95% CI 0.6 to 6.2)
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in these studies.
- Side effects were not reported as an outcome in these studies.
- No deaths were reported in these studies.

NITRAZEPAM VERSUS ACTH

There was one study Dreifuss 1986[4].

- Effects on psychomotor development was not reported as an outcome in this study.
- Effects on subsequent seizure rates was not reported as an outcome in this study.
- Effects on cessation of spasms was not reported as an outcome in this study.
- Effects on time taken to achieve cessation of spasms was not reported as an outcome in this study.

- Effects on reduction in the number of spasms: Dreifuss 1986 showed an >50% reduction in spasms in 66% of the group treated with nitrazepam compared with 50% in the group treated with ACTH, Peto odds ratio 2.0 (95% CI 0.7 to 5.9).
- Effects on relapse rates was not reported as an outcome in this study.
- Effects on time taken to relapse was not reported as an outcome in this study.
- Effects on resolution of hypsarrhythmia was not reported as an outcome in this study.
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in this study.
- Side effects: Dreifuss 1986 had to withdraw ACTH in six patients, hypertension and maleana were given as two causes for withdrawal.
- Deaths: Dreifuss 1986 had one patient in their ACTH group who died, but no cause was found at autopsy.

METHYSERGIDE VERSUS ALPHA-METHYLPARATYROSINE

There was one study Hrachovy 1989[7]

- Effects on psychomotor development: Hrachovy 1989 used the Denver Developmental Screening Test to evaluate developmental status at entry into the trial and at 3 weeks post entry into the trial. They stated, in their results section, that two patients in each group showed developmental improvement but did not quantify this further. They did not report developmental status at 3 months post trial entry or at 5 years of age.
- Effects on subsequent seizure rates was not reported as an outcome in this study.
- Effects on cessation of spasms: Hrachovy 1989 found only one patient (8%) treated with methysergide and two (16%) treated with alpha-methylparatyrosine responded to therapy, Peto odds ratio 0.5 (95% CI 0.1 to 5.2).
- Effects on time taken to achieve cessation of spasms was not reported as an outcome in this study.
- Effects on reduction in the number of spasms: Hrachovy 1989 showed a >50% reduction in spasms in 25% of the group treated with methysergide compared with 17% in the group treated with alpha-methylparatyrosine, Peto odds ratio 1.6 (95% CI 0.2 to 11.2).

- Effects on relapse rates: no patient treated with methysergide remained spasm free and only one of the two patients successfully treated with alpha-methylparatyrosine remained spasm free. Peto odds ratio 0.14 (95% CI 0.0 to 6.8).
- Effects on time taken to relapse was not reported as an outcome in this study.
- Effects on resolution of hypsarrhythmia was not reported as an outcome in this study.
- Effects on time taken to achieve resolution of hypsarrhythmia was not reported as an outcome in this study.
- No side effects severe enough to warrant stopping treatment were reported in this study.
- No deaths were reported in this study.

Discussion

Infantile spasms were first described 160 years ago in a letter that Dr West wrote to the Lancet. Since that time at least 30 drugs have been tried and reported in the literature, but treatment remains problematic and the long-term prognosis remains poor for both psychomotor development and subsequent development of other seizure types. Despite the wealth of literature on this subject there have been only a few RCTs and the majority of studies have been either open prospective or retrospective trials. The RCTs that have been undertaken contain only small numbers of subjects with the result that they have little or no power and have used widely varying dosage regimes and outcome measures, making meta-analysis difficult to perform. In addition, only eight drugs out of all those used in the treatment of infantile spasms have been subjected to RCTs. We found no RCTs comparing forms of therapies, such as phenobarbitone or pyridoxine, despite the fact that these are often first line therapies in some countries. Some therapies (for example gamma-globulins, pyridoxine, lamotrigine) have been reported as case reports or in uncontrolled trials. We have not considered these therapies in this review. In addition many different "steroid" preparations have been used in the available RCTs. This is partly due to the availability of different compounds in different countries, for example in Europe and Japan synthetic ACTH is usually available, whilst in the USA natural ACTH derivatives are normally used. ACTH can only be given as an injection, intramuscularly, intravenously or into the peritoneal cavity, infants find this distressing and many centres use oral preparations such as prednisone or hydrocortisone in preference. This makes analysis of the efficacy of individual "steroid" preparations difficult.

Despite an extensive literature search we found only ten RCTs and the overall reported methodology was poor. Only one study had considered the number of patients required to determine whether one treatment was more efficacious than another; they based their calculations on the assumption that the trial drug would be 50% more efficacious in stopping the spasms than the comparative drug; their trial did not find such a difference. Although all the studies claimed to be randomised, less than half stated how randomisation had been performed and only two studies stated that adequate concealment of randomisation had taken place. Ideally to minimise performance bias trials should be double-blinded, although perhaps it is not surprising that only two such trials have been performed. Blinding the recipients (or parents) and staff administering the therapies remains problematic. ACTH can only be given by intramuscular injection, whilst the other drugs used in the above RCTs are administered orally and nowadays it is generally considered to be unethical to administer placebo intramuscular injections to young infants. In addition, many of the side effects of steroids are common and easily recognised, for example weight gain and hypertension, making blinding difficult. Some would also argue that it is possible that the spasms are directly linked to the development of severe learning difficulties and it is generally thought (though not proven) that it may be possible that the earlier the spasms are brought under control the better the outcome. Thus delaying treatment (for example by administering placebo alone) is also usually thought to be unethical. Finally five studies had loss of patients to follow up and the remaining studies did not clearly state that all patients entered into the trials had been successfully followed up for the duration of the study. We had also planned to look for possible sources of clinical heterogeneity between the studies, for example, sex, age at spasm onset, age at trial entry, delay to treatment and whether or not participants had received previous treatment. Unfortunately, this information was not available for the majority of the included studies and we are unable to draw any conclusions. However, it is possible that some of these sources of heterogeneity are important in determining outcome. For example, the study Baram 1996 found ACTH to be more efficacious than prednisolone but had three times as many girls than boys in the ACTH group and roughly equal numbers in the prednisone group. It is possible therefore, that if girls have a better outcome than boys that this may have contributed to the differences seen in response between their two groups.

When developing our protocol we had tried to provide definitions for terms such as infantile spasms, cessation of spasms, relapse etc. We had planned to try and establish

whether different definitions used by authors for infantile spasms might affect which participants would be included into a trial, thereby affecting outcome. It became clear from our review of the literature that few authors clearly define the term infantile spasms and it was clear that some trials using entry criteria that defined the need for hypsarrhythmia in fact entered infants who did not have this. It is theoretically possible that either some patients entered into these trials did not have infantile spasms or that different trials were investigating different populations. Therefore, for the purpose of this review we accepted that any RCT stating that their participants had "infantile spasms" would be included, but the results should be interpreted with caution. Likewise, we had also tried to define outcome measures such as cessation of spasms and what constituted a relapse, so that we could accurately compare the outcomes of each individual study. Again, the majority of studies did not define such outcomes and meta-analysis of these outcomes should again be interpreted with caution.

Infantile spasms are associated with a poor long-term prognosis. The majority will also have severe learning difficulties, with high cost implications not only to the patients and the families and their quality of life, but also on health services. Therefore, if any one treatment was proven to improve long-term psychomotor development and to reduce the risk of further seizure types then it would probably be considered to be more efficacious than other treatments regardless of the effect on the spasms themselves or the hypsarrhythmia. Although, with time the spasms will resolve, many patients continue to have other forms of epilepsy into adult life and about one fifth will progress to Lennox Gastaut syndrome. These patients will therefore require anticonvulsants and will continue to suffer the effects of epilepsy, often for life. However, no study has considered these factors as long term outcome measures beyond 44 months post trial entry, and currently there is no standard agreement on the timing or means of measuring these outcomes.

The spasms themselves are certainly distressing to parents and carers. It is possible that they are also distressing to the infant as many will cry immediately following a spasm or appear to be in pain and distressed, so much so, it is not uncommon for the spasms to be mistaken for colic. Whilst the long-term benefits of different therapies remain uncertain, we tried to establish if any one therapy was more efficacious in stopping the spasms themselves. One small study looking at patients with infantile spasms and an underlying diagnosis of tuberous sclerosis found vigabatrin to be more efficacious than hydrocortisone

in stopping the spasms in this group of patients, a finding also found in some open studies[53]. However, it is not clear that vigabatrin is more efficacious than steroids in treating infantile spasms in patients without tuberous sclerosis. One underpowered RCT showed a trend that vigabatrin might be more efficacious than placebo. Two small studies, Baram 1996 and Hrachovy 1993, did show ACTH to be more efficacious than prednisone in stopping the spasms, however their dose of prednisone of 2mg/kg/day would be considered too low a dose by some and it is therefore possible that higher doses of prednisone may be as efficacious as ACTH[54]. Further trials are required. We found no other RCTs comparing other forms of therapies, such as sodium valproate, benzodiazepines, pyridoxine or phenobarbitone, in terms of cessation of spasms. Although four studies did consider reduction in the number of spasms, it is not at all clear as to whether a reduction in spasms is of major benefit to a patient. Complete control of spasms has to be the main objective. Some open, prospective trials have suggested that vigabatrin might control spasms more quickly than steroids. Only three RCTs considered the time taken to cessation of spasms and there was no significant difference between vigabatrin and hydrocortisone or ACTH.

The exact relationship between clinical spasms and typical or even modified (or atypical) hypsarrhythmia on the EEG is not entirely clear. Not all infants with clinical evidence of infantile spasms have hypsarrhythmia, and in those in whom it is present it is not always present all of the time. It is not known whether the presence or absence of hypsarrhythmia affects long term outcome. Again we had hoped that by collecting and combining data from the studies, it might help clarify these areas of uncertainty. Unfortunately, few studies contained sufficient data to draw any conclusions.

We had also planned to look at subgroup analysis of clinical features, but unfortunately, because of lack of trials this was not possible. It was possible to consider patients with an underlying diagnosis of tuberous sclerosis as a subgroup in one underpowered study. This study, Chiron 1997[3] showed vigabatrin to be more efficacious than hydrocortisone in stopping the spasms in this group of patients. All their patients treated with vigabatrin had complete cessation of spasms and only one patient relapsed within the study period. However, the numbers are small - only eleven patients in each group and these results should be treated with caution, even though this result mimics the findings of open studies. Further trials are required with larger numbers of patients to confirm (or refute) the

findings of this study.

Side effects must always be taken into account. Any drug with unacceptable side effects will not be used in clinical practice. Likewise if two drugs show similar beneficial effects then the one with the safer drug profile should be used in preference. Within these studies few side effects or deaths were reported. However, both steroids and vigabatrin have potentially serious side effects. The problem with steroids are potentially life threatening problems which include depression of the immune system and modified response to infection leading to overwhelming sepsis. Less serious side effects, for example hypertension, are often transient but nevertheless have the potential to cause morbidity. Minor side effects, estimated to occur in two thirds of patients, include behavioural changes especially irritability, changes in appetite, weight gain and alteration in sleep patterns. In addition some forms of steroids (e.g. ACTH) involve daily intramuscular injections. However, there have been reports of both asymptomatic and symptomatic visual field defects with loss of peripheral vision to varying degrees in adults and children treated with vigabatrin. It appears to occur most commonly in patients who have been treated with vigabatrin for more than six months but it does not appear to always be reversible on withdrawing the vigabatrin. The main difficulty in infants is that they cannot be tested or monitored for visual field defects (a child needs to be at least eleven to be able to co-operate and complete a reliable test). However, on balance the devastating effects of infantile spasms probably outweigh the risks of developing the severe side effects of these therapies.

Implications for practice

The optimum treatment for infantile spasms remains uncertain. No study to date has shown any one drug to be more efficacious than any other in terms of long term psychomotor development or subsequent epilepsy rates. Vigabatrin may be more efficacious than placebo, and ACTH may be more efficacious than low doses of prednisone in stopping the spasms. Vigabatrin may be more effective than hydrocortisone in stopping the spasms in the group of patients who also have tuberous sclerosis. We found no one treatment to be more efficacious than any other with regard to reduction in number of spasms, relapse rates or resolution of hypsarrhythmia. Both steroids and vigabatrin have potentially serious side effects but the risks of these should be considered against the potential benefits, when considering treatment of infantile spasms.

Implications for research

There is still little evidence available on the optimum treatment for infantile spasms. Further trials with improved methodology, standardised valid outcome measures, larger numbers of participants and longer follow up are required. As stated previously infantile spasms are a relatively rare disorder, so that in order to be able to recruit large numbers of patients into randomised controlled trials, multicentre collaboration is likely to be required.

References

See appendix three

CHAPTER SIX

Oral treatment of non-convulsive status epilepticus in tuberous sclerosis

Age of seizure onset is one of the most important prognostic factors for long-term outcome in patients suffering from TSC. It is rare for patients who have normal development and intellect at the age of five who subsequently develop epilepsy to regress. In the review of the patients in the Bath region over the past ten years no patient who developed fits over the age of five had impaired intellect. One unusual cause of regression after the age of 5 years in TSC is the development of non-convulsive status epilepticus (NCSE). The epilepsy in TSC is often refractory to treatment and NCSE is regularly seen in those whose seizures are most difficult to treat. In addition these patients are liable to suffer recurrent attacks of NCSE.

Dr Frank Besag, National Centre for Young People with Epilepsy, has treated his patients with NCSE with oral diazepam for many years. He recommended this treatment to JPO who also had success with oral diazepam treatment of NCSE in some of his TSC patients. A literature search of the English Language failed to find any studies looking at this form of treatment or comparing it with conventional intravenous benzodiazepine administration.

NCSE is an infrequent but severe epileptic seizure disorder. It is characterised by a patient who has continuous or almost continuous epileptic activity both clinically and on EEG but the clinical signs of an epileptic seizure disorder may be extremely subtle. Usually, but not always in a patient with NCSE, there is a history of a previous overt seizure disorder, frequently severe. This can include IS and other difficult to control epileptic syndromes including Lennox-Gastaut syndrome. Clinically there is no clonic jerking of the limbs and although the patient may have some awareness of their surroundings, impaired consciousness is the main clinical feature. The onset may either be so subtle as to suggest a dementia or may be abrupt. Lack of awareness may extend to loss of appetite with significant weight loss. Patients may cycle from periods of complete unresponsiveness to one of partial responsiveness. Frequent brief, but small, myoclonic jerks can often be felt but not seen: they are random in time and site and are effectively detected clinically by a light handshake. Often there are associated autonomic features such as excessive salivation, sweaty palms and pupils that are rapidly dilating and constricting for no obvious reason.

Aim

Prolonged periods of impaired consciousness can interfere with development, education and well-being. The traditional treatment, effective in the majority of cases of idiopathic primary generalised NCSE, is the intravenous administration of benzodiazepines [114], which requires hospital admission and is inappropriate for those with frequently recurring attacks.

Therefore, the aim of this study was to evaluate the use of oral diazepam in aborting attacks in those with recurrent episodes of NCSE.

Method

The notes of all the patients seen in the Bath Tuberous Sclerosis Clinic in 1996 (including patients outside the Wessex region) were examined to identify those patients who had a history of NCSE. The diagnosis of NCSE was made on clinical grounds at the time of attending the clinic as defined above; palpable myoclonic jerks, evidence of autonomic dysfunction and impaired consciousness were all required before NCSE was diagnosed. Those notes were then examined further to ascertain the patient details, information about their epilepsy and the treatment received. No patients were excluded from the study because of lack of data in the medical notes.

Results

Eight patients had a history of NCSE, including the two patients reported in chapter two, five males and three females. All eight patients had presented with IS by the age of seven months. They all subsequently developed secondarily generalised tonic-clonic seizures, absence seizures and drop attacks.

The age of onset of the NCSE varied from six to 18 years. The clinical nature of the episodes varied greatly. For example the parents of case four described a picture of being 'limp, lethargic, lying around, dribbling, often staring and gazing with pupils dilated, hands sweating, unusual circulation and jerky movements of the limbs'. Case three had an insidious onset over three to four months during which time he had changed from being independently mobile to becoming wheelchair bound. On occasions when he did walk, he would walk into doors. He also became disinterested in food during this period, lost weight and was thought to be terminally ill when referred. He was given 10mg oral diazepam and within an hour was alert and had a normal appetite. The dose was repeated when NCSE recurred; on average every five days, with the same effect and speed of action.

Seven were treated successfully with oral diazepam (table seventeen) and in only one (case number five) was drowsiness, lasting about three hours, noted to be a problem. No other side effects were recorded. The dose of diazepam required varied considerably and bore no relationship to either the child's age or weight, but was the dose required to produce

clinical evidence of the abolition of NCSE (a return of consciousness, an absence of both myoclonic jerks and signs of autonomic dysfunction) as determined by the parents or carers. Confirmation, of the diagnosis of NCSE and of its abolition on EEG was only available by direct observation and investigation for one of the patients who was subsequently admitted and suffered an episode of NCSE whilst on the ward, in our hospital.

Table seventeen

	Age NCSE diagnosed	**Sex**	**Dose (mg)**	**Effect of diazepam**	**Prophylactic anti-convulsant treatment (total / day)**
Case 1	6 years	Female	30	Markedly reduces time of NCSE (from days to hours)	Sodium Valproate 1200mg Phenobarbitone 90mg
Case 2	9 years	Male	5	Aborts NCSE	Sodium Valproate 1000mg* Carbamazepine 1800mg
Case 3	13 years	Male	10	Aborts NCSE within 1 hour	None #
Case 4	14 years	Female	10 – 20	Aborts NCSE	Sodium Valproate 1800mg Nitrazepam 7.5mg
Case 5	16 years	Male	10	Aborts NCSE	Carbamazepine 1200mg Vigabatrin 2.5g
Case 6	18 years	Female	5	Markedly reduces time of NCSE (from days to hours)	Carbamazepine 1200mg Vigabatrin 750mg Nitrazepam 5mg
Case 7	27 years	Male	20-40	Aborts NCSE	Sodium Valproate 800mg Carbamazepine 1200mg Lamotrigine 200mg
Case 8	3 years	Male		Not known – admitted in non-convulsive status elsewhere and given iv diazepam	Sodium Valproate 900mg Vigabatrin 1g

*** This boy was later inadvertently given 4000mg sodium valproate / day and his NCSE recurred, responding to a reduction in dose to 1000mg/day**

 # This boy had not been on any anticonvulsants for 8 weeks prior to treatment for his NCSE as he was considered "terminally ill" . Previously he had been tried on at least 8 different anticonvulsants to try and control his seizures, without obvious benefit.

This table shows the outcome of treatment with oral diazepam in the seven patients. One patient did not receive an oral dose.

The eighth patient diagnosed as having episodes of NCSE, from the parent's description in clinic, was prescribed 5 mg oral diazepam to be given at the onset of the next episode to see if it would abort the attack. He was then admitted to his local hospital with NCSE before the oral diazepam was given (he too had the clinical diagnosis of NCSE confirmed by EEG). After successful treatment with IV diazepam he was discharged and to date (three years later) has had no further episodes: his other seizures have also reduced in frequency.

Discussion

These eight patients with TSC all had a severe recurrent epileptic seizure disorder and were on regular prophylactic anticonvulsant treatment. We do not know if their EEG would have supported a diagnosis of primary generalised or secondarily generalised NCSE except in two patients. However we agree with Aicardi[115] that a generalised EEG in these patients who at other times have focal EEG changes and who have tubers causing focal structural lesions makes it difficult to decide on classification. Our diagnoses were made on clinical grounds and it was not possible to further validate this: there must therefore be some doubt about the diagnosis of NCSE and of its abolition. However we believe these diagnoses are usually reliable clinically and the response to treatment would support this. An EEG is preferable but was usually not possible in our cases: it would be required if the diagnosis were in doubt. Our patients were usually recognised as having episodes of NCSE between attacks when in clinic either on history alone or history supported by examination at the time. Carers were taught what to look for so that the diagnosis could be confirmed during a telephone consultation. These latter are a common practice in our TSC clinic because of the need for frequent feedback concerning the epilepsy and the great distance some people travel to visit the clinic.

Little has been published about NCSE and many paediatricians are unfamiliar with its clinical signs, diagnosis or management. In most publications intravenous diazepam is the usual treatment for NCSE, effective in 80-100% cases of primary NCSE but only 15 – 59% of secondary NCSE[116]: this is not convenient when the patient suffers recurrent attacks, because of the severity of their epileptic seizure disorder, despite appropriate regular anticonvulsant treatment. Oral diazepam is not normally considered for antiepileptic treatment since it is not effective for the termination of primary generalised tonic-clonic

seizures or for prophylaxis because an inability to achieve adequate blood levels. Oral diazepam has been used to prevent febrile convulsions and other agents, buccal or nasal, midazolam most frequently, have more recently been used for primary generalised status epilepticus. Why it might work in NCSE is unclear. We have found it to be effective in patients with TSC for recurrent attacks of NCSE that the parents and carers can learn to recognise, so allowing prompt treatment to be given without necessitating hospital admission. It is likely to be equally or more effective in primary generalised NCSE.

Side effects were only seen in one patient. Effective management of NCSE in these patients has allowed planned alteration to regular anticonvulsant treatment without admission to hospital, making it easier for carers to consider trying alternative prophylactic anticonvulsant management. In one patient the inadvertent administration of large doses of sodium valproate (>100mg/kg) re-precipitated recurrent attacks of NCSE, which resolved on return to the prescribed dose: no other associations between NCSE and prophylactic treatment were noted. Precipitation of NCSE by a rapidly increasing dosage of sodium valproate in an adult patient has been previously described [117].

Conclusion

Oral diazepam is a safe and effective treatment for termination of NCSE in patients with TSC. If parents and carers can be taught to recognise episodes of NCSE early in their evolution so that early intervention with oral diazepam can be undertaken thus abolishing the attacks then the outcome may be improved and regression avoided. Unfortunately all the patients in this series had suffered severe fits from a young age and had severe learning difficulties at the time of onset of their NCSE and it is difficult to ascertain whether further regression has been avoided in these patients.

CHAPTER SEVEN

Lymphangioleiomyomatosis and Tuberous Sclerosis

Lymphangioleiomyomatosis (LAM) is thought to occur as a complication in approximately 1% of patients with TSC. Although Lutembacher first described LAM in association with TSC in 1881, he mistook the cystic and nodular changes for metastasis from renal fibrosarcoma, in the lungs of a 36 year old woman who died from bilateral pneumothoracies. It wasn't until 1939 that Berg and Vejilens gave the first accurate and clear description of the clinical and radiological features of pulmonary tuberous sclerosis. It is difficult to estimate the true incidence of LAM in TSC, other than it is undoubtedly rare, partly because the few studies that have attempted to do so have generally used small numbers of patients from biased groups and partly because it is unknown how many patients with pulmonary complications become symptomatic and are therefore recognised. In 1971 Dwyer et. al.[118] described three cases and reviewed the literature on a further 31 cases and in 1995 Castro et al.[44] produced a retrospective study of nine patients seen at the Mayo Clinic in the previous 43 years. The other reports have all been of only a few patients.

LAM is a rare cystic lung disease that is usually generalised and progressive, can be extremely difficult to treat and has generally been considered to have a poor prognosis. It has almost exclusively been reported to occur in women of childbearing age, the commonest presentation being dyspnoea and pneumothorax, after which many patients follow a relentless deterioration. Although LAM is a rare complication of TSC it causes a significant amount of morbidity and mortality.
LAM predominately affects females of childbearing age[119]. The commonest presenting symptoms are dyspnoea and pneumothorax but other symptoms include chronic cough, haemoptysis, chylothorax, wheeze and chest pain. Cyanosis, respiratory failure and cor- pulmonale also occur[44 118 119]. Asymptomatic cases have also been described, with radiographic changes being the only clue to pulmonary involvement[118]. Pulmonary function tests tend to show an obstructive pattern although a restrictive pattern has been noted in some patients[120].
Treatment of LAM is difficult, and historically it has been treated symptomatically, for example, drainage of pneumothoracies, conventional inhalers for wheeze and oxygen therapy for respiratory failure. More recently hormone manipulation has been tried with variable success[44, 121] The long-term prognosis is considered poor with many patients following a relentless deterioration after the onset of their symptoms[118].

Aims

Despite the fact that LAM has been recognised as a complication of TSC for over 80 years and is the third commonest cause of premature mortality, after renal disease and brain tumours[32], it is probably under recognised, its epidemiology and natural history remains poorly understood and there is little data on the effectiveness of treatment or the value of

screening. Therefore, the aim was to try and highlight those patients at greatest risk of developing LAM in TSC and to try and provide further guidance for both the screening and the treatment of this entity.

Methods – To ascertain patients with LAM in TSC

Patients suffering from the pulmonary complications of TSC were identified from several sources;

1. The Bath TSC clinic, research and epidemiological studies: clinical information was available on 145 patients known to suffer from TSC in the Wessex region and on approximately 250 other TSC patients from outside the Wessex region.
2. By contacting all the respiratory physicians in the Wessex region asking them to notify us of any patients with LAM who might also have TSC.
3. The Tuberous Sclerosis Association (TSA).
4. The medical genetics department in Cardiff.
5. The renal department in Brighton, where a TSC clinic is held.

Patients were classified as having LAM on the following criteria;

1. **A definite diagnosis**
   (a) Pathological confirmation by lung biopsy.
   (b) Pathological confirmation at post mortem.
2. **A probable diagnosis**
   (a) Typical findings on HRCT scan i.e. the presence of multiple thin walled cysts.
   (b) Honeycombing +/- pneumothorax on CXR.
   (c) Fine reticular shadowing +/- pneumothorax on CXR.
3. **A possible diagnosis**
   (a) pneumothorax only on CXR.

Patients were accepted as having TSC according to strict interpretation of the recently revised criteria for clinical diagnosis: i.e. at least one hamartoma present in each of a minimum of two different organs (but excluding the lung for the purpose of this study)[4].

The following information was then collected by visiting each patient (other than those deceased), studying their clinical notes and obtaining copies of the relevant investigations;

- Age of diagnosis of TSC.
- Diagnostic criteria for TSC.
- Family history of TSC.
- Age at presentation of lung disease.
- Age at diagnosis of lung disease.

- Mode of presentation.
- Pulmonary symptoms and complications.
- Chest X-ray (CXR), high resolution computerised tomography (HRCT) and biopsy findings.
- Any disturbance in spirometry.
- Extrapulmonary manifestations (renal in particular).
- Treatment undertaken.
- Outcome.

Results

Ascertainment of patients

Three patients from Wessex had been diagnosed as having LAM, two of who were deceased.

22 out of the 23 (96%) respiratory physicians in the Wessex region replied, but only one had a patient with both LAM and TSC and this was the live patient that had been identified from above.

The TSA was then contacted for the names of any patients suffering from the lung complications of TSC and an advertisement placed in SCAN, the association's publication. Thirteen additional patients were contacted in this way including the names of two patients who had died from their disease.

Three patients were known to the medical genetics department in Cardiff.

A renal physician in Brighton, who knew of our interest, then gave us the names of two further patients bringing the total to twenty-one.

Confirmation of diagnosis

Definite LAM: We gave ten of our patients a definite diagnosis of LAM. These included the four patients (patients 1-4) in whom a pathological diagnosis of LAM was confirmed at post-mortem and the six patients (patients 5-10) who underwent open lung biopsy. In these patients the histology was reported as consistent with LAM (i.e. proliferation of smooth muscle), honeycomb lung or as having multiple cysts and bullae.

Probable LAM: Six patients (patients 11-16) had HRCT of the chest with findings consistent with LAM. Three other patients had abnormal CXRs suggesting LAM, two (patients 17 & 18) had a honeycomb appearance and one (patient 19) fine reticular shadowing and on the grounds of this together with the clinical history were given a probable diagnosis of LAM.

Possible LAM: The remaining two (patients 20 & 21) had evidence of pneumothoracies but no other abnormality on CXR and therefore were given a diagnosis of possible LAM only.

TSC: All our patients, other than patient 21, had facial angiofibroma (a hamartoma considered pathognomonic of TSC) plus the presence of at least one hamartoma in another organ (for example renal AML, retinal phakoma, giant cell astrocytoma, or subependymal nodules) and had a definite diagnosis of TSC. Patient 21 had two hypomelanic macules together with a strong family history of TSC: both her sister and son had been diagnosed as having definite TSC (and her mother who had not been screened was known to have ungual fibromata) thus making her a likely obligate carrier. Unfortunately the patient herself had not undergone fundoscopy, renal or cranial imaging in order to prove the diagnosis of TSC and was therefore given a diagnosis of probable, rather than definite TSC.

Population characteristics (table eighteen)

There were 18 females and 3 males.

The median age of diagnosis of TSC was 17 years with a range of 6 weeks to 37 years. Three (patients 7, 9 and 10) had a diagnosis of TSC made as a result of their respiratory disease; the others had a variety of reasons. Seven had a family history of TSC, five of whom had the diagnosis of TSC made as a result of a child being diagnosed. This gives a spontaneous mutation rate of 66%.

Table eighteen

Patient	Sex	Age at diagnosis of TSC	Reason for diagnosis of TSC	Age of diagnosis of Pulmonary symptoms	Presenting feature(s)
Patients with a definite diagnosis of LAM					
1	Female	16 years	Retinal phakoma	25 years	Pneumothorax (bilateral)
2	Female	4 years	Facial angiofibroma CT brain	18 years	Pneumothorax
3	Female	2 years	Infantile spasms CT brain	18 years	Pneumothorax (bilateral)
4	Female	3 years	Epilepsy CT brain	19 years	Pneumothorax
5	Female	9 months	Facial angiofibroma	7 years	Dyspnoea
6	Female	37 years	Investigated following diagnosis of son	Teenager	Dyspnoea and chest pain
7	Male	6 months	Pulmonary TSC	6 months	Thick pulmonary secretions
8	Female	18 months	Infantile spasms CT brain	21 years	Pneumothorax (bilateral)
9	Female	34 years	Pulmonary TSC	10 years	Dyspnoea and weight loss
10	Female	30 years	Pulmonary TSC	30 years	Pneumothorax (bilateral)
Patients with a probable diagnosis of LAM					
11	Female	21 years	Investigated following diagnosis of daughter	34 years	Dyspnoea
12	Female	11 months	Infantile spasms CT brain	19 years	Pneumothorax
13	Female	5 years	Facial angiofibroma CT brain	32 years	Pneumothorax
14	Female	35 years	Renal haemorrhage	38 years	Chylothorax
15	Female	17 years	Investigated following diagnosis of son	17 years	Pneumothorax (bilateral)
16	Female	37 years	Ungual fibroma on feet Angiofibroma	23 years	Pneumothorax
17	Female	24 years	Investigated following diagnosis of son.	20 years	Pneumothorax
18	Male	6 weeks	Epilepsy CT brain	8 years	Dyspnoea and dry cough
19	Male	21 years	Epilepsy CT brain	32 years	Pneumothorax
Patients with a possible diagnosis of LAM					
20	Female	6 years	Facial angiofibroma	20 years	Pneumothorax
21	Female	28 years	Obligate carrier Two hypomelanic patches	25 years	Pneumothorax

Table showing the sex of each patient, the age at which TSC was diagnosed and the reason for diagnosis of TSC, the age of onset and the presenting features of the pulmonary disease, stratified by definite, probable and possible diagnosis of LAM.

Pulmonary disease

The average age of onset of pulmonary symptoms was 19 years with a median of 20 years and a range of birth to 34 years. The average age of diagnosis of pulmonary tuberous sclerosis was 25 years with a median of 25 years and a range of six months to 38 years. On average there was a delay of six years between the onset of respiratory symptoms and the eventual diagnosis of LAM.

The commonest presenting feature was pneumothorax, which occurred in 14 of the patients, five of whom presented with bilateral pneumothoracies. Five patients had a history of gradual onset dyspnoea. One patient presented with a chylothorax. The final patient had thick bronchopulmonary secretions requiring suction as an infant: a lung biopsy at the age of six months gave the diagnosis of LAM (table eighteen).

Pulmonary symptoms: 19 patients complained of dyspnoea, 15 had a cough with six having haemoptysis at times, 13 patients experienced pain usually, though not always, in conjunction with proven pneumothoracies and 11 patients noticed wheezing at times (table nineteen).

Complications

In total 17 of the 21 patients suffered pneumothoracies. There were 12 right sided, five left sided and six bilateral pneumothoracies. Four patients suffered from chylothoraces, one had a pericardial effusion and one died from pulmonary haemorrhage (table nineteen).

Four patients died as a result of their respiratory disease:

> The first patient had sudden onset of pain and shortness of breath at the age of 25 years. She was diagnosed as having bilateral pneumothoracies requiring bilateral pleurodesis. There was then a gradual deterioration over the following 20 years with increasing shortness of breath, a productive cough and cyanosis. She was initially treated with home oxygen but was later admitted to a long stay hospital where she developed cor-pulmonale and died at the age of 47 years from her lung disease. She was considered for a lung transplant but it was decided that, because of her history of pleurodesis and her general medical condition by that stage, she would be unable to tolerate the operation.

The second patient had had a history of a left pneumothorax, aged 18 years, which was treated by pleurodesis. Three years later she had bilateral pneumothoracies, which were again treated by pleurodesis. Approximately a year later she complained of shortness of breath and started suffering from recurrent chest infections. She then developed respiratory failure requiring increasing amounts of oxygen therapy. Although hormonal treatment was tried it was ineffective and at the age of 26 years she too was considered for a lung transplant. Unfortunately by that time she was so weak it was felt that she would not be able to tolerate the physiotherapy required. In addition there were technical concerns because of the pleurodesis. She died a year later.

The third had been admitted for investigation of indigestion and vomiting and underwent gastroscopy under general anaesthetic. During the procedure she developed bilateral pneumothoracies and required admission to intensive care. The pneumothorax on the right failed to resolve and chemical pleurodesis was performed. Following this her urinary output deteriorated and she went into renal and respiratory failure, dying one week later.

The fourth patient was a 19 year old girl with a history of severe renal involvement. She had a one week history of dyspnoea and dry cough (following two recent airplane flights) and had been treated by antibiotics before presenting to casualty with a left-sided pneumothorax. She was treated conservatively and allowed home to await HRCT and review. Two days before her review she suffered an acute fatal pulmonary haemorrhage whilst asleep.

One other patient also had a history of respiratory failure with two respiratory arrests as a result of developing pneumonia after a 10 year history of gradually increasing shortness of breath. She was treated in hospital with oral steroids and oxygen. She was not ventilated because there were concerns about the possibility of not being able to wean her off a ventilator. She has since made a remarkable recovery and just six months later has returned to work.

Table nineteen

Patient	SOB	Cough	Haem	Pain	Wheeze	Complications	CXR	HRCT	Biopsy / histology
Patients with definite LAM									
1	✓	✓		✓		1 Bil. P.	P.	Not performed	"lung involvement"
2	✓	✓		✓		1 Bil. P.	P.	Unavailable	Appearance of LAM
3	Developed bilateral pnuemothoracies under GA and died whilst ventilated 7 days later.						P.	Not performed	LAM
4	✓	✓				1 Lt P, 1 Chy, 1 Pul. Haem.	P.	Not performed	LAM
5	✓	✓	✓	✓		2 Rt P.	P. RS.	Multiple cystic spaces	Proliferation of immature muscle.
6	✓		✓	✓		2 Rt P. 1 Lt P.	P.	Not performed	Small cysts in the lung tissue
7		✓			✓		H.	Not performed	Appearance is that of LAM.
8	✓	✓			✓	1 Bil. P, 1 Chy	P.	Not performed.	Proliferation of smooth muscle.
9	✓			✓	✓	1 Rt P, 1 Chy, 1 CE.	Emph.	Emphysema	Opinion is of honeycomb lung.
10	✓	✓		✓	✓	1 Bil P.	P.	Consistent with LAM	Proliferation of smooth muscle.
Patients with a probable diagnosis of LAM									
11	✓	✓		✓	✓		H	Thin walled cysts.	Not performed
12	✓	✓	✓		✓	1 Rt P.	P.	Lung cysts and bullae.	Not performed
13	✓	✓		✓		1 Rt P.	P.	Honeycomb pattern	Not performed
14	✓					1 Chy	P. Eff.	Cystic changes of TSC	Not performed.
15	✓			✓	✓	1 Bil P.	P.	Thin walled cysts.	Not performed
16	✓	✓		✓	✓	1 Rt P, 1 Lt P.	H.	Thin walled cysts	Not performed
17	✓	✓	✓	✓	✓	2 Rt P, 1 Lt P.	H.	Not performed	Not performed
18	✓	✓	✓		✓		H.	Not performed	Not performed
19	✓	✓		✓		1 Rt P.	RS	Not performed	Not performed.
Patients with a possible diagnosis of LAM									
20	✓	✓	✓	✓	✓	1 Rt P.	P.	Not performed.	Not performed
21	✓					1 Lt P.	P.	Not performed	Not performed

SOB = dyspnoea, Haem = Haemoptysis, CXR = chest Xray, HRCT = high resolution computerised tomography scan of chest.
Rt P. = right pnuemothorax, Lt P. = left pnuemothorax, Bil P. = bilateral pnuemothorax, Chy = Chylothorax, Pul Haem = pulmonary haemorrhage, CE = cardiac effussion,
P. = pnuemothoxax, R.S. = reticular shadowing, Emph = emphasema, Eff = pleural effusion.

Table showing the symptoms and the complications experienced and the investigations undertaken on each patient.

Investigations (table nineteen)

All four patients who died as a result of their lung disease had post-mortem examination of their lungs. In all cases the histology was consistent with a diagnosis of LAM and TSC.

Six patients underwent open lung biopsy reported as being consistent with LAM.

Nine patients had undergone HRCT all of which demonstrated the well-defined thin wall cysts characteristic of LAM (see figure eighteen).

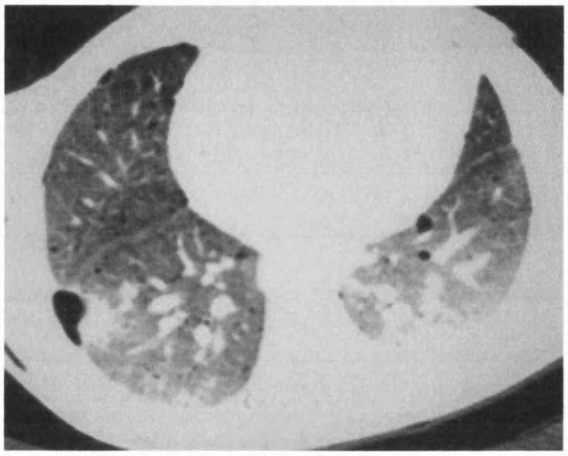


Figure eighteen: HRCT chest of patient with LAM

All 21 patients had undergone CXR during the course of their illness. Seventeen had evidence of pneumothoracies and four showed pleural effusions. In addition six demonstrated a picture of nodular shadowing or honeycombing, and two had fine reticular shadowing (figure nineteen).

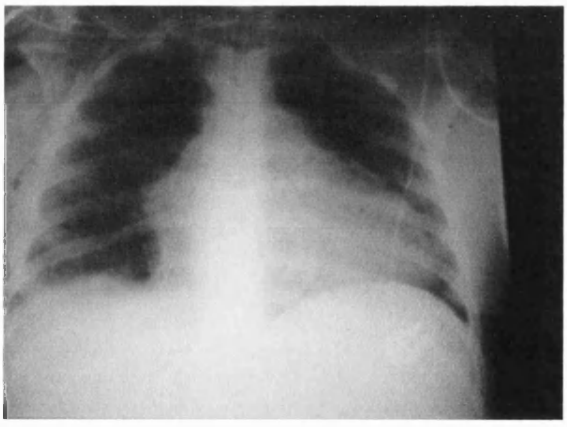


Figure nineteen: CXR showing honeycombing in a patient with LAM

It was not possible to perform spirometry on ten of the patients; four who had had died, five who had severe learning difficulties and were unable to co-operate with the test and the spirometer was not available at the time of the visit of one further patient. Lung function tests in the remaining patients were normal in two, showed an obstructive picture in three and a restrictive pattern in the other six.

Treatment (table twenty)

Drainage of the pneumothoracies and chylothoraces was undertaken in the acute phase when necessary. Nine patients underwent pleurodesis and four pleurectomy for recurrent or severe pneumothoracies.

Five patients were prescribed conventional inhalers with little or no improvement in symptoms.

Four patients received progesterone therapy;

Patient two suffered her first pneumothorax at the age of eighteen, which was treated by pleurodesis, three years later she had bilateral pneumothoracies, again treated by pleurodesis. A year later aged 22 years she began to suffer from increasing dyspnoea and recurrent chest infections. She was commenced on progesterone tablets but her condition continued to deteriorate and the progesterone was discontinued after one year. She later died aged 27 years.

Patient ten had bilateral pneumothoracies aged 30 years requiring pleurodesis. She was then started on depot provera, which she has continued to the present day (five years follow up). Since starting the progesterone she has remained well with mild dyspnoea and wheeze on exertion and an occasional cough (no haemoptysis) only.

Patient twelve suffered her first pneumothorax aged twenty one requiring pleurectomy. Over the following 16 years she had slowly worsening dyspnoea with episodes of haemoptysis. At the age of 35 years a HRCT of the chest confirmed the diagnosis of LAM and depot provera was commenced. Over the following year her exercise tolerance improved and she also showed an improvement in spirometry. She remains well on the depot provera.

Table twenty

	Acute / surgical treatment	Long term Medical treatment	Disease Course (follow up)
Patients with a definite diagnosis of LAM			
1	Drainage Pleurodesis	Oxygen therapy	Died from cor-pulmonale whilst waiting for transplant (~ 25 years after onset of symptoms)
2	Drainage Pleurodesis	Oxygen therapy Progesterone	Died from cor-pulmonale, too ill for transplant (~ 10 years after onset of symptoms)
3	Drainage and ventilation	None	Died from respiratory and renal failure (~ one week after onset of symptoms)
4	None	None	Died from massive pulmonary haemorrhage (~ two weeks after onset of symptoms)
5	Drainage Pleurodesis	None	Stable (3 years)
6	Drainage Pleurectomy	None	Remains well (25 years)
7	None	Inhalers (no benefit)	Improved (23 years)
8	Drainage Pleurectomy	None	Remains well (6 months)
9	Lobectomy	None	Remains well (38 years)
10	Drainage Pleurodesis	Progesterone	Remains well (6 years)
Patients with a probable diagnosis of LAM			
11	None	Atrovent (little benefit)	Stable (13 years)
12	Drainage Pleurectomy	Progesterone	Improved (18 years)
13	Drainage Pleurodesis	Atrovent (some benefit)	Remains well (2 years)
14	Drainage	Progesterone	Remains well (1 year)
15	Drainage Pleurodesis	None	Progressive deterioration (10 years)
16	Drainage Pleurodesis	Inhalers (no benefit)	Progressive deterioration (30 years)
17	Drainage Pleurodesis		Progressive deterioration (31 years)
18	None	Inhalers (little benefit)	Improved slowly (6 years)
19	Aspiration	None	Remains well (2 years)
Patients with a possible diagnosis of LAM			
20	Drainage Pleurodesis	None	Remains well (17 years)
21	Drainage	None	Remains well (5 years)

Table showing acute surgical and medical treatment, long term medical treatment, disease course and time of follow up.

Patient fourteen suffered a renal haemorrhage at the age of 35 years, which was treated conservatively by transfusion. She was then commenced on depot provera but four years later suffered a pneumothorax and chylous effusion, treated by drainage. She continues with hormonal treatment.

A course of steroids (dexamethasone / prednisolone) was prescribed for two patients with no discernible effect on the progression of their disease. Though a third patient suffering from acute respiratory failure made a remarkable recovery after treatment with oxygen and steroids.

The two patients who died from cor-pulmonale received home oxygen therapy and courses of antibiotics when appropriate. Both these patients were also considered for lung transplantation.

Follow up (table twenty)
Two patients died within a few weeks of developing respiratory symptoms.

The remaining patients were followed up for an average of 14 years and a median of 10 years (range 6 months to 38 years).

Five patients have shown a progressive deterioration, a further two dying from their disease. Three patients have improved slowly whilst two have remained stable. The other nine patients have remained well with no further symptoms occurring after treatment of their presenting symptoms.

Skin manifestations
All the patients had skin manifestations of TSC. Twenty patients had facial angiofibroma, 19 hypomelanic patches, 12 ungual fibromas, 11 a shagreen patch, eight a fibrous forehead plaque, eight nail ridging, five skin tags, three had poliosis and three confetti depigmentation.

Renal manifestations (table twenty-one)
Twelve (57%) patients had a clinical history of renal involvement; of those who did not only three had undergone imaging of the kidneys of whom one was found to have

angiomyolipomas (AML). Post mortem examination of a patient who had also been entirely asymptomatic also showed evidence of renal disease. One patient died as a result of a combination of renal and respiratory failure.

In total five patients suffered from proven haemorrhage, one underwent nephrectomy, one had embolisation performed and one required both embolisation and then nephrectomy.

The other two patients were treated conservatively, one by transfusion the other with analgesia and antibiotics.

In addition two patients had embolisation, and one a nephrectomy performed for pain relief. One patient had a presumed renal carcinoma removed that was subsequently shown to be an AML on histology.

Neurological manifestations

Epilepsy was the commonest neurological manifestation occurring in 18 (86%) of our patients at some time. Ten (48%) patients had associated learning difficulties, but in three it was very mild and they had been able to attend mainstream school. Six (29%) patients had associated behavioural problems – autistic tendencies and hyperactivity. Two patients had a GCA diagnosed with associated hydrocephalus requiring tumour excision and shunt insertion. One patient had a mild hemiplegia.

Other clinical associations

Four patients (patients 7,11,18,19) had scoliosis, two were fixed and two were mobile, none had undergone surgery or bracing. All four patients have had a relatively mild course of LAM. Pulmonary function was only possible in one patient. He had a mild restrictive defect, so although scoliosis is known to affect pulmonary function, it is difficult to assess what part it has played in the respiratory disease of these four patients.

Four patients were also incidentally noted to have hepatic haemangioma on USS or CT scan. None had a history of cardiac rhabdomyomas or WPW syndrome.

Table Twenty-one

	Renal complications	Age of onset of symptoms	Pain	Haematuria	Haemorrhage	USS / CT result	Treatment
Patients with a definite diagnosis of LAM							
1	Asymptomatic					Not done	
2	Pain	11 years	Yes	Yes	Yes	Not known	Embolisation and nephrectomy
3	Pain, ARF	15 years	Yes			Multiple AML	
4	Pain	16 years	Yes		Yes	Multiple AML	Embolisation
5	UTIs	Unknown		Yes		Multiple AML	
6	Asymptomatic					Not done	
7	Asymptomatic					Normal	
8	Asymptomatic					AML and cysts	AML removed
9	Asymptomatic					Not done	
10	Asymptomatic					Not done	
Patients with a probable diagnosis of LAM							
11	Pain, UTIs	Childhood	Yes			AML & cysts	
12	Pain	20 years	Yes			Multiple AML	Embolisation
13	Asymptomatic					Not done	
14	Pain	35 years	Yes		Yes	Bilateral AML	Transfusion
15	Pain	Not known				AML & cysts	
16	Pain	21 years	Yes			Normal R kidney	Nephrectomy
17	Haemorrhage	14 years	Yes	Yes	Yes	Cysts R kidney	Analgesia and antibiotics
18	Asymptomatic					Not done	
19	Pain	32 years	Yes			AML & cysts	Embolisation
Patients with a possible diagnosis of LAM							
20	Pain, UTIs	11 years	Yes	Yes	Yes	AML & cysts	Nephrectomy
21	Asymptomatic					Normal	

Table showing the renal symptoms, complications and investigations of our group of patients.

Methods - Literature search (see appendix four for references)

A search of the English literature for all cases of LAM, both with and without associated TSC, was performed from 1939 to 1997 using the Medline database and from 1981 to 1997 using the EMBASE database. The references of all retrieved papers (including those discounted after review) were searched for additional references.

The cases were then divided into four groups on the following criteria:
TSC: the paper either stated that a diagnosis of tuberous sclerosis had been made in the individual(s) or gave enough features in the individual(s) to fulfil the diagnostic criteria for tuberous sclerosis (for example the combination of epilepsy, mental retardation and renal angiomyolipoma).
Possible: the paper did not state whether the individual(s) did or did not have tuberous sclerosis but described some features suggesting the possibility that they might have TSC (e.g. renal angiomyolipoma or mental retardation).
Unlikely: the paper did not state that the diagnosis of tuberous sclerosis had been excluded and did not describe any features of tuberous sclerosis in the individual(s).
Not TSC: The paper clearly stated that the individual(s) did not have any features of tuberous sclerosis. How this was done was not always stated.

Results

In total there were 183 papers citing a total of 445 individual cases of LAM.

83 cases had **TSC,** 119 were **possible** cases, 174 cases were **unlikely** and 69 definitely were **not TSC**.

Population characteristics

There were 435 females, 9 males and in one case the gender was not given.
78 females and 5 males had TSC, 117 females and 2 males had possible TSC, 172 females, 1 male and one other patient (gender not stated) were unlikely to have TSC and 68 females and 1 male were stated as not having TSC.

Pulmonary disease

The average age of onset of pulmonary symptoms was given for 365 / 445 (82%) cases and was 32.7 years with a range of 4 years to 70 years.
TSC: Given for 75 patients, Average = 30.4 years (range = 8 – 57 years, SD = 9.2 years).
Possible: Given for 74 patients, Average = 27.5 years (range = 4 – 59 years, SD = 10.7 years).
Unlikely: Given for 148 patients, Average = 35.6 years (range = 4 – 70 years, SD = 11.5 years).

Not TSC: Given for 68 cases, Average = 34.6years (range = 9 – 62 years, SD = 11.9 years).

The average age of diagnosis of LAM was given for 273 / 445 (61%) cases and was 36.2 years with a range of 4 – 72 years.
TSC: Given for 59 patients, Average = 36.6 years (range = 13 – 72 years, SD = 10.7 years).
Possible: Given for 50 patients, Average = 34.3 years (range = 4 – 61 years, SD = 13.4 years).
Unlikely: Given for 135 patients, Average = 36.6 years (range = 14 – 72 years, SD = 10.7 years).
Not TSC: Given for 29 cases, Average = 36.6 years (range = 8 – 68 years, SD = 12.7 years).

Therefore on average there was a delay of 3.5 years between the onset of respiratory symptoms and the eventual diagnosis of LAM.

The presenting features were given for 320 / 445 (72%) patients (see table twenty two) and there was a wide range of pulmonary symptoms described in all groups (also summarised in table twenty two). Pneumothorax and chylothorax were the commonest reported complications. Pleural effusions were also reported but it was not always stated whether these were serous, chylous or bloody.

Investigations and confirmation of diagnosis of TSC

Only two thirds of the papers stated how a diagnosis of LAM was confirmed. In the papers that did, the majority were confirmed either histologically (post mortem or biopsy) or by CT scan. Lung function testing was only performed on / given for approximately half of the patients in the literature (table twenty three).

Table twenty two

	TSC n = 83	Possible n = 119	Unlikely n = 174	Not TSC n = 69
Dyspnoea any time:	67 %	66%	85%	91%
Dyspnoea at presentation:	38%	46%	59%	20%
Pneumothorax any time:	47%	56%	36%	67%
Pneumothorax at presentation:	29%	35%	21%	68%
Cough any time:	24%	43%	42%	35%
Cough at presentation:	0%	3%	11%	0%
Chylothorax any time:	10%	27%	27%	33%
Chylothorax at presentation:	2%	8%	4%	2%
Haemoptysis any time:	19%	20%	23%	32%
Haemoptysis at presentation:	0%	5%	1%	3%
Respiratory failure any time:	0%	0%	0%	0%
Respiratory failure at presentation:	0%	0%	0%	2%
Pain (without proven pneumothorax) **any time:**	6%	8%	2%	2%
Pain (without proven pneumothorax) **at presentation:**	0%	0%	0%	0%
Other any time:	2%	1%	13%	3%
Other at presentation:	6%	0%	1%	2%
Asymptomatic	25%	3%	4%	3%

Table showing the symptoms suffered at any time by, and the presenting symptoms of, the patients in each of the four groups.

Table twenty three

	TSC n = 83	Possible n =119	Unlikely n = 174	Not TSC n = 69
Investigations (for diagnosis)				
Post mortem	9 (10%)	0	17 (10%)	8 (12 %)
Biopsy	18 (21%)	48 (40%)	84 (48%)	16 (23%)
Chest CT	15 (18%)	9 (8%)	61 (35%)	7 (10%)
CXR	9 (10%)	15 (13%)	2 (1%)	4 (6%)
Pulmonary function tests				
Normal	5 (6%)	3 (3%)	9 (5%)	4 (6%)
Obstructive	18 (22%)	18 (15%)	46 (26%)	16 (23%)
Restrictive	3 (4%)	3 (3%)	19 (11%)	1 (1%)
Mixed	0	0	10 (6%)	33 (48%)
Abnormal	8 (10%)	0	4 (2%)	2 (3%)

Table showing the investigations undertaken (and method of diagnosis) and the pulmonary function tests.

Treatment and outcome

Where stated most patients were treated symptomatically. pneumothoracies and effusions were drained when clinically necessary and pleurodesis and pleurectomies were frequently reported. Many patients received courses of antibiotics and those in respiratory failure were treated by oxygen.

Hormonal manipulation was tried in a total of 187 / 445 (42%) of patients with variable success (table twenty-four).

Unfortunately progression of the disease was only given for 95 / 258 (37%) of patients who did not receive hormonal manipulation as treatment and even fewer gave an indication of how long the patients had been followed up, but the findings are summarised in table twenty-four.

Table twenty-four

Patients who did undergo hormonal manipulation					
	TSC n = 83	**Possible n = 119**	**Unlikely n = 174**	**Not TSC n = 69**	**Total n = 445**
Improved	6 (33%)	2 (6%)	19 (20%)	2 (5%)	29 (16%)
Stable / unchanged	5 (27%)	1 (3%)	27 (28%)	9 (21%)	42 (22%)
Worsened / died	6 (33%)	26 (81%)	47 (50%)	23 (55%)	102 (55%)
Unknown	1 (5%)	3 (9%)	2 (2%)	8 (19%)	14 (7%)
Total	18	32	95	42	187
Average follow up	5 years	10 years	4 years	8 years	
Patients who did not undergo hormonal manipulation					
	TSC n = 83	**Possible n = 119**	**Unlikely n = 174**	**Not TSC n = 69**	**Total n = 445**
Improved	0	2 (11%)	1 (3%)	1 (7%)	4 (5%)
Stable / unchanged	6 (24%)	3 (17%)	12 (32%)	3 (20%)	24 (25%)
Worsened / died	19 (76%)	13 (72%)	24 (65%)	11 (73%)	67 (70%)
Total	25	18	37	15	95
Average follow up not given for this as data not available					

Table showing the effects of hormonal manipulation on the course of the disease (compared with patients who did not receive hormonal manipulation).

Discussion

Diagnosis of LAM

We divided our group of patients into those who we felt had a definite (patients 1 –10), a probable (patients 11- 19) and a possible (patients 20& 21) diagnosis of LAM. Although our numbers were small there were no discernible differences between these three groups

in terms of presentation, clinical course and outcome. Unfortunately, when searching through the literature it was not always clear as to how the diagnosis was reached or how unequivocal the diagnosis was. For the purpose of our review we have assumed that the diagnosis of LAM is correct in all the literature cases. However it must be borne in mind that some cases may have been misdiagnosed and therefore suffer from other diseases such as fibrosing alveolitis that have similar clinical and radiological appearances.

It is also interesting to note that papers have used the terms lymphangiomyomatosis and lymphangioleiomyomatosis synomonously to describe the changes in the lung. Histologically, there is proliferation of irregularly arranged, spindle-shaped smooth muscle cells surrounding the lymph channels and blood vessels within the lung parenchyma. There is no evidence of fat cells or collections in the lesions[122 123 124 125 126], therefore this condition is most appropriately described as lymphangioleiomyomatosis.

Diagnosis of TSC

We divided our group of patients into those who had a definite diagnosis of TSC, according to the strict criteria given above, and those who had a probable diagnosis only. For the purpose of the literature review we divided the patients on the information given by the individual paper. For example, if a paper stated that the patient had TSC then they would be classified as having TSC. Again it must be borne in mind that some cases may have been misdiagnosed.

Prevalence

The Bath epidemiology study knew of 147 patients on 1st January 1997 with a diagnosis of TSC in the Wessex region. The population of the Wessex region obtained from the Office of Population Census and Surveys is 3,400,000. This gives a prevalence rate within the Wessex region of 1:23,500 and this figure is similar to that found by other studies estimating the prevalence of TSC. We know we are likely to have missed some cases of TSC[1 19], but within our population we are less likely to have missed symptomatic LAM. On 1st January 1997 there was only one live TSC patient in the Wessex region, known to have LAM, giving a prevalence rate of 0.66%, but patient four who was also alive at that time had asymptomatic LAM. This is similar to previous studies. Dwyer et. al.[118] and Torres et al[127] (found 3 cases out of 403 patients reviewed) estimated that symptomatic LAM occurs in less than 1% of patients with TSC. Castro et. al.[44] believe their series

shows the incidence to be slightly higher at around 2.3%. However, incidental findings of LAM have been described on the CXRs and CT scans of entirely asymptomatic patients[118]. No study has been undertaken to screen TSC patients for LAM and it is likely that the true prevalence is higher than 1%.

Population characteristics

LAM predominately affects females of child bearing age although cases occurring in men[128] and children[129 130 131] have rarely been reported. In many cases symptoms start or are exacerbated during the menstruation period or in the course of a pregnancy[132 133]. Patients have also reported onset of symptoms following the menopause, or after commencing the oral contraceptive pill[134 135].

We had 18 females and three males in our group of 21 patients. All the female patients developed symptoms prior to the menopause. One (patient ten) had onset of respiratory symptoms during her first pregnancy when she suffered bilateral pneumothoracies. Two developed respiratory symptoms prepubertally at the age of seven (patient five), with dyspnoea, pain haemoptysis and pneumothoracies, and at ten (patient nine) with dyspnoea, pain, wheeze, pneumothorax and chylothorax (both started their menses in their teens). Both these patients subsequently had open lung biopsy performed with a definite diagnosis of LAM, so confirming that LAM in TSC is not confined to females of childbearing age.

In the literature out of 360 female cases in whom an age of onset was given there were five cases of onset in childhood (4, 9, 9, 12 and 13 years). In total 7 / 378 cases presented in childhood: approximately 2%.

We also had three phenotypic males in our group who exhibited signs of lung disease. Two of the males developed symptoms at an early age: six months and eight years.

> The first boy had a very unusual presentation; from birth he suffered from thick pulmonary secretions requiring frequent suction and recurrent chest infections. At the age of 6 months he underwent lung biopsy that was reported as showing LAM. The combination of this result with the history of epilepsy and developmental delay led to the diagnosis of TSC. During childhood he continued to have recurrent chest infections requiring antibiotic treatment but

since going through puberty his infections have become far less frequent. He has never suffered from pneumothoracies, chylothoraces or haemoptysis. Unfortunately, the lung biopsy is no longer available for repeat analysis in order to confirm the diagnosis and he is not sufficiently co-operative to undergo HRCT. His unusual course must throw some doubt on the diagnosis.

The second male patient had suffered from episodes of dyspnoea and wheeze from the age of eight years. He was originally diagnosed has having asthma, but asthma medication did not relieve his symptoms and a CXR showing honeycombing confirmed the diagnosis of LAM. He has never suffered from pneumothoracies, chylothoraces or haemoptysis. He has never had confirmation of LAM made by HRCT or open lung biopsy.

The third male had been entirely asymptomatic until the age of 32 years when he suffered a spontaneous pneumothorax, which required treatment with drainage only, he has had no recurrence (follow up 4 years), nor suffered any other respiratory symptoms. His HRCT showed thin walled cysts and his CXR reticular shadowing of the lung fields suggestive of LAM. Interestingly on testing his chromosomes his genotype was 47XXY (Klienfelters syndrome). This may give an explanation of his presentation of a lung disease that is normally limited to females.

Looking through the literature there are five reported cases[46 118 129 136] of LAM in TSC males and a further possible two cases[128 137]. Their clinical, radiographic and histology details are summarised in table twenty- five.

Case one: had CXR findings compatible with a diagnosis of LAM and a lung biopsy reported as "consistent with TSC".
Case two: had CXR findings that were not typical of LAM and had not had CT or biopsy performed. It is therefore possible that this patient did not have LAM.
Case three: had findings typical of LAM on his CXR, but the authors did not state whether the biopsy showed smooth muscle proliferation.
Case four: although given a definite diagnosis of TSC, in the text the only features described were skin tags and café au lait spots: we would not accept

these as confirming the diagnosis of TSC, so this diagnosis should be accepted cautiously.

Case five: given that HRCT is highly sensitive at showing the thin walled cysts associated with LAM, the presence of a normal result should make the diagnosis unlikely.

In case six the authors stated that the biopsy was consistent with LAM but described a proliferation of lymph vessels rather than smooth muscle hyperplasia. These findings may be compatible with a diagnosis of lymphangioma rather than lymphangioleiomyomatosis.

Case seven only had a clinical diagnosis of LAM.

Table twenty- five

	Clinical Findings	CXR	CT Scan	Biopsy
Patients diagnosed as having TSC				
Case 1[118]	Dyspnoea	Extensive reticular changes	Not given	Consistent with TSC
Case 2[118]	Dyspnoea	Ill defined opacity plus a cyst	Not given	Not given
Case 3[138]	Dyspnoea Pneumothorax	Pneumothorax and cysts	Not given	Thickened pleura and cysts
Case 4[136]	Dyspnoea and cough	Not given	Not given	Cysts, empty or filled with fluid
Case 5[46]	Dyspnoea	Pleural effusion	Did not show pulmonary alterations	Not given
Patients with a possible diagnosis of TSC				
Case 6[128]	Pleural effusion	Pleural effusion	Not given	Abnormal proliferation of lymph vessels Consistent with LAM
Case 7[137]	Pleural effusion, pneumothorax	Not given	Not given	Not given

Table showing possible cases of LAM in males in the literature

It is therefore difficult to estimate the true frequency of LAM in TSC males, other than it must be extremely rare. In any male in whom the diagnosis is suspected, other pulmonary diagnoses must be considered and excluded and

chromosomal analysis undertaken. Patients should have HRCT at the very least and preferably lung biopsy performed to confirm the diagnosis.

Although the numbers are small, the findings hint at the possibility that the clinical course of LAM in TSC is milder in males than females.

The average age of diagnosis of TSC in our group of patients was 17 years, slightly older than that usually seen for TSC. This may be a chance finding because of the small numbers, but it may also back previous observations that patients with pulmonary TSC generally suffer milder forms of TSC often delaying diagnosis. For example; Singerland et al.[138] found TSC patients without LAM to have intellectual impairment in 46% of cases and seizures in 93%. In the patients with LAM 20% had intellectual impairment and 62% had seizures.

Pulmonary disease

We found the average age to onset of pulmonary symptoms, and the subsequent diagnosis of LAM to be earlier than that cited in the literature although the delay between onset and diagnosis was similar. With regard to Dwyer's[118] data this difference may be explained, at least in part, by improved diagnostic imaging and increased awareness over the past 25 years that lung complications do occur in TSC. However Castro[44] et al had similar findings to Dwyer[118] in their review just two years ago (though they only had nine cases). The average age of onset of pulmonary symptoms in our group of patients was 19 years and diagnosis 25 years. This compares to an average of 30.4 and 36.6 years in the patients with TSC in the literature. In both groups there is a delay of about 6 years between onset and diagnosis. Therefore, the earlier age of diagnosis found in our small group of patients may just reflect a chance finding of earlier age of onset.

Comparing LAM in patients with TSC to those without TSC there is a later age of onset of symptoms (30.4 and 34.6 years respectively) and shorter period of delay between onset and diagnosis in the group without TSC. This difference might be explained by the Knudson two hit therory[10]: normally for a tumour to arise (in an individual without an inherited defect), two independent somatic mutations are required, explaining why sporadic tumours in those without TSC can rarely arise in a single tissue later in life. But individuals who have already inherited an inactivated tumour suppressor gene only need one further

somatic mutation to lose both alleles, explaining why in TSC the tumours often occur earlier.

Histologically the lungs show perivascular and perilymphatic smooth muscle throughout the lung fields. The proliferation of the smooth muscle gives rise to the different clinical manifestations depending on its site. For example, around the airways it leads to obstruction and air trapping contributing to the obstructive picture on lung function testing and also causes bullae formation leading to pneumothoracies and a restrictive picture on lung function testing. Around the pulmonary venules it leads to venous congestion with consequent haemoptysis and around the arterioles it may precipitate pulmonary hypertension and cor-pulmonale, whilst involvement of the lymphatics may lead to chylothorax. In addition there is also proliferation of fibrous tissue which probably contributes to the diffusion impairment seen in the most affected patients whilst, shunting and V.Q. mismatching may increase the degree of hypoxia[44 139].

As alluded to above, pulmonary tuberous sclerosis can present in a multitude of guises. Presentation can range from mild exertional dyspnoea to sudden acute severe respiratory distress with marked hypoxia and collapse. One common scenario is that described by Slingerland[138] in his case presentations of a 21 year old daughter and her 45 year old mother. Progressive dyspnoea begins in the 2nd or 3rd decade of life accompanied by a chronic non-productive cough and haemoptysis; this is then followed by the onset of increasing number of lower respiratory tract infections associated with worsening hypoxemia and an obstructive respiratory picture. Death can occur within years as a result of respiratory failure and cor-pulmonale. In another case presentation of a 21 year old girl by Uzzo et al[140], the patient had been entirely asymptomatic from a respiratory point of view until 2 weeks prior to scheduled surgery for renal angiomyolipoma. She then presented as an emergency with a massive left pneumothorax and bilateral chylothorax eventually requiring several chest drains and bilateral pleurectomies.

We also found a wide range of presentation from gradual onset of shortness of breath to sudden bilateral pneumothoracies, thick pulmonary secretions to chylothorax. The commonest presenting symptoms were pneumothorax and dyspnoea. Other symptoms included; chronic dry cough, haemoptysis, wheeze, and chest pain. Development of

cyanosis, respiratory failure and cor-pulmonale was also common. These corresponded to the findings in the literature.

Chylothoracies may occur less commonly in patients with TSC, 10% of cases with proven TSC compared to 33% in patients in whom TSC has been definitely excluded. A possible explanation may be differences found histologically as the smooth muscle proliferation in LAM seen in TSC is more frequently described as being predominantly peri-vascular; in LAM without TSC it is peri-lymphatic[122 123 124 125 126]. The reason for these differences is not clear. Pneumothoracies seem to be equally common in both forms of the disease.

We also report two rare manifestations of LAM. The first is the occurrence of a pericardial effusion (patient nine). This patient presented at the age of ten with dyspnoea and weight loss. She subsequently developed recurrent pleural effusions, a persistent right pneumothorax and a pericardial effusion. She was treated by lobectomy after which all her symptoms resolved and she has remained well since. There has only been one other case[141] reported in the literature in a patient without TSC. She had a history of dyspnoea and recurrent pneumothoracies and had been diagnosed as having LAM on biopsy. She then presented with cardiac tamponade and was found to have a haemopericardium, which was successfully treated, by a subdiaphragmatic window. The second rare manifestation was patient four who suffered a massive pulmonary haemorrhage resulting in sudden death. To our knowledge this has not been previously reported in the literature.

Lymphangioleiomyomatosis is described as a generalised lung disease affecting all zones of the lung equally[142]. However, we believe that, in patients with TSC at least, there is evidence that it can occur as a focal entity. This is best demonstrated by the clinical history of two of our patients. Patient nine (described above) had severe persistent disease for several years until she underwent a lobectomy, following which her symptoms resolved. She has received no other treatment and has remained asymptomatic for 38 years. Patient six also had a two year history of severe persistent disease with dyspnoea, haemoptysis, pain and recurrent pneumothoracies. She then underwent pleurectomy, has had no other treatment, and has developed no further symptoms in 25 years of follow up.

Investigations

A CXR is the first investigation, showing any pneumothoracies, chylothoraces and effusions and excluding other causes: it may show prominent interstitial markings with obvious cysts sometimes forming a honeycomb pattern and in milder cases may show a microreticulonodular pattern often greatest in the lower lobes[118 139]. Nevertheless, in the early stages the CXR may be unhelpful.

In these cases, HRCT is more sensitive and more precise at demonstrating the well-defined cysts that tend to have smooth thin walls. The architecture of the intervening lung tissue is normal. Occasionally focal markings due to lymphatic oedema in the alveoli and intralobular septa secondary to lymphatic involvement are also seen[143 144]. HRCT also has the advantage of correlating better with lung function than plain radiography[145]; disease extent as rated independently on a scale 0%-100% of involvement on HRCT, correlated significantly with impairment in gas exchange (using carbon monoxide diffusion). There was no significant correlation between the number of opacities seen on CXR and the results of any of the pulmonary function tests. It is frequently stated that HRCT is highly sensitive in diagnosing LAM and in combination with a clinical history and examination, open lung biopsy to confirm the diagnosis may only rarely be required[146]. Also there have been two reports[147 148] of diagnosis made on cytology following aspiration of chylous effusion. In both cases immature smooth muscle cells and surface cells from the endothelium were demonstrated, suggesting that the LAM tissue had ruptured into the thoracic cavity. In both cases the diagnoses were later confirmed by open lung biopsy.

Only one case has been cited in the literature on the use of magnetic resonance imaging (MRI) in LAM. King[149] reported on a 33-year-old woman who underwent MRI because of the possibility of chest wall recurrence of breast cancer. An incidental finding was focal areas of low signal intensity surrounded by thin walls. HRCT gave a diagnosis of LAM, which was later confirmed by open lung biopsy. There is no reference in the literature as to the use of MRI either in the diagnosis or as a marker of response to treatment in pulmonary tuberous sclerosis.

Spirometry

Spirometry shows wide ranging of patterns from normal to obstructive through mixed to restrictive. This variation is unsurprising when the underlying pathogenesis is considered.

Initially there is proliferation of smooth muscle cells around the bronchi leading to narrowing of the lumen, as seen in asthma, giving rise to an obstructive picture. Unlike asthma the narrowing is not due to bronchospasm but rather hyperplasia, and the obstruction is not readily reversible. With time, air trapping in the alveoli leads to an emphysematous picture with the formation of cysts and bullae giving rise to a restrictive picture. As the disease progresses with more smooth muscle cells surrounding both the airways and the blood vessels, diffusion becomes impaired, cor-pulmonale and respiratory failure develop.

Clinical associations

Because very few studies (none of them large) of patients with LAM in TSC have been described in the literature it is difficult to accurately summarise its associations with the other clinical stigmata of TSC. Some authors have suggested that pulmonary TSC tends to develop in patients with less severe disease, especially when considering seizures and learning difficulties[44 118 138]. In Castro's[44] study eight out of nine of patients suffered from severe renal disease with haemorrhage into AML prior to diagnosis of their lung complications, suggesting a possible association between symptomatic renal disease and LAM.

We carefully looked for other clinical associations of TSC in our 21 patients and compared them with the 250 patients known to have TSC in the Wessex region to see if there was any phenotype at high risk of developing LAM. If this proved to be the case it might form a basis for screening high-risk patients. There was no significant difference between the two groups in the prevalence of any of the following stigmata / clinical associations of TSC;

- skin manifestations,
- epilepsy,
- learning difficulties,
- behavioural problems,
- renal disease,
- cardiac disease.

We also took blood from all our patients in order to analyse whether genotype correlates with lung disease but this data will not be available for some time. We therefore propose, that at the present time, there are no prognostic factors that assist in predicting which

individuals with TSC are at greatest risk of developing lung disease, but that it is rare in men and children.

Treatment

Again, because of the rarity of this condition few studies have been performed to assess long-term treatment and indeed few therapeutic measures have been undertaken in order to ameliorate the course of the disease. Instead treatment is symptomatic, treating the complications as they arise. Pneumothoracies and chylothoraces are treated in the acute phase by drainage, though pleurodesis is often required, as they are frequently recurrent. Chest infections are treated with the appropriate antibiotics and haemoptysis, if severe, occasionally requires iron supplements. The cough and wheeze are difficult to control as they are generally caused by the proliferation of the smooth muscle, (though undoubtedly some patients do have an element of bronchospasm), with the result that conventional inhalers are often ineffective. In those patients with a chronically deteriorating course, continuous oxygen therapy will be required towards the terminal stages of the respiratory failure and cor-pulmonale.

The presence of hormone receptors in the lung tissue of patients with LAM and TSC,[150 151], the suggestion that exacerbations can occur at times of hormonal fluctuation for example during pregnancy and in association with the oral contraceptive pill, and the relative absence of LAM in males have, not surprisingly, led to attempts to ameliorate the disease by hormonal manipulation[121 152 153 154 155].

In the literature review just under half of patients were tried on hormonal therapy. They used a wide range of therapies including oophrectomy, radioablation of the ovaries, progesterone administration and androgens with varying results. The best results are seen in those patients with TSC. One third of patients with TSC tried on hormonal therapy showed improvement compared with none showing improvement without hormonal treatment, although the numbers are small and consist mainly of individual cases in open studies.

In 1989 Eliasson et al[121] undertook a meta-analysis of the hormonal treatment of LAM. They identified 30 cases of LAM treated by hormonal manipulation. Unfortunately many

of the cases lacked information on dosage, timing and duration of therapy making them ineligible for inclusion in the analysis. (table twenty-six).

Table twenty-six[121]

Hormonal therapy	Claimed success	Cases excluded*	Objective success
Progesterone alone	8/13	5	5/9
Oophrectomy alone	5/9	2	5/7
Tamoxifen alone	2/7	4	1/3
Androgen alone	0/1	0	0/1
Oophrectomy + progesterone	3/5	3	2/2
Oophrectomy and tamoxifen	0/1	1	0
Progesterone + tamoxifen	½	2	0
Oophrectomy, progesterone + Tamoxifen	1/3	1	1 /2

Reported regimens of treatment before and after meta-analysis.
***In sequential evaluation of each case, ten case were excluded because therapy was started too late in the course of disease; six additional cases were excluded due to lack of data on dosage; and of cases remaining, two were excluded due to insufficient data to judge outcome of therapy**

The remaining studies showed oophrectomy alone or in combination with progesterone to be the most successful therapeutic option with seven out of nine cases showing stabilisation or improvement. Progesterone alone was successful in five out of nine patients. None of the other regimes showed any significant benefit. Although this review suggests that hormonal manipulation might be beneficial in some patients the results need to be treated with caution. It is not clear if any of the thirty cases reviewed suffered from TSC and it is not yet known whether LAM with TSC and LAM without TSC are similar in their response to treatment. In addition it appears that the natural history of LAM in TSC is extremely variable. Finally, we would not recommend radioablation of the ovaries as a means of hormonal manipulation in patients with TSC: the genes involved in TSC are tumour suppressor genes so there is a theoretical risk (at least) that exposure to radiotherapy may increase the incidence and development of hamartomas. Our series would not alter these findings.

Angel Ferdnandez-Gonzalez[156] suggested in 1993 that lung transplantation should be considered in patients in view of poor survival after the onset of respiratory symptoms. Sadly, previous pleurectomies and the presence of systemic disease (cor-pulmonale,

hypertension etc), not to mention lack of donors, limits the number of patients in whom this is a viable option. It is also impossible to predict at the onset of symptoms, which patients will follow a relentless deteriorating course, which patients will remain relatively stable or even improve spontaneously and those who will respond to hormonal treatment. In addition, there have been reports of LAM recurring in transplanted lungs[157 158].

Outcome

LAM is an important cause of mortality in TSC. In the review undertaken by Charles Shepherd et. al.[32] at the Mayo Clinic in 1991 lung disease was the fourth commonest cause of early mortality in TSC, accounting for four out of 49 deaths, despite it only affecting 1 – 2.5 % of all TSC sufferers.

It was previously thought that there was a relentless and severe deterioration after the onset of the disease. Average duration of survival was reported to be 4.8 years in 1971[118]. More recent studies estimate survival times to be nearer to 10 years and some reports have even told of spontaneous resolution of the disease. In our experience the clinical course in TSC is extremely variable, with death occurring within days of the onset of symptoms in some patients, whilst others may remain asymptomatic for years.

Screening

Screening for LAM in patients with TSC remains controversial. We had hoped to highlight those patients at greatest risk of developing LAM and propose a screening model for this complication; however this has not been possible. The criteria required for a good screening programme include (as taken from Health For All Children edited by David Hall – please see box below [203, 204]):

1. A recognisable latent or early symptomatic stage; this does not appear to be the case with LAM. Fourteen of our patients presented acutely with pnuemothoracies having been previously asymptomatic, two died within a short period of time.
2. That the natural history of the development of the disease from latent to symptomatic disease should be understood; further research is required for this.
3. There should be a suitable test for detecting the disease at an early or latent stage, which should be acceptable to the population; HRCT is likely to be the most sensitive tool for recognising LAM but it is not clear that changes are seen on HRCT before the development of symptoms and it may be unwise to screen all

females approaching childbearing age in view of the radiation dose administered in patients with TSC who already have one mutation of their tumour suppressor gene; we had considered if lung function testing, spirometry or oxygen saturation, could be used for screening, these are simple non-invasive tests that can easily be performed in a clinic setting, however even in our small cohort of patients with symptomatic disease there was wide variation in lung-function suggesting that it is unlikely to be helpful as a screening tool.

4. There should be an acceptable form of treatment available for the disease, which if administered at the presymptomatic stage of the disease should favourably influence its course and prognosis; as discussed above further research is required to assess the efficacy of treatments such as progesterone in this group of patients, before it could even be considered to be given in pre-symptomatic patients.

However, it may be worth considering assessment in female patients of child bearing age for lung disease before they undergo anaesthesia or fly as these may precipitate onset of symptoms.

Criteria for screening programmes[203, 204]
1. The condition being sought should be an important health problem for the individual and the community.
2. There should be an acceptable form of treatment for patients with recognizable disease or some other form of useful intervention should be available (e.g. genetic counselling).
3. The natural history of the condition, including its development from latent to declared disease, should be adequately understood.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination for detecting the disease at an early or latent stage, which should be acceptable to the population.
6. Facilities should be available for diagnosing and treating patients uncovered by the programme.
7. there should be an agreed policy on whom to treat as patients.
8. The treatment at the pre-symptomatic stage of the disease should favourably influence its course and prognosis.
9. The cost of case finding which should include the cost of diagnosis and treatment, should be economically balanced in relation to (a) possible expenditure on medical care as a whole and (b) the cost of treatment if the patient does not present until the disease reaches a symptomatic stage.
10. Case finding should be a continuing process, not a once and for all project.

Conclusion

LAM is a rare but important cause of morbidity and mortality in patients with TSC. Importantly, the only risk factor we found both in our cohort of patients that it almost exclusively occurs in female patients of childbearing age. It may rarely occur in prepubertal girls, the diagnosis should strongly be questioned in males. We found no other prognostic factors to identify those female patients at greatest risk of developing the disease, but some authors have suggested an association between symptomatic renal disease and LAM. We did not find any other clinical manifestations to be more common in our group of TSC patients compared with the overall population of TSC patients. LAM is usually generalised but may be focal in some patients and has a highly variable clinical course and again we found no prognostic factors to predict how the disease will progress in any individual, or those patients who will benefit from treatment. However, it does appear that hormonal manipulation may be beneficial in as many as one third of patients and further clinical trials are needed to fully evaluate the efficacy of such treatments. At present there is no evidence that screening the whole TSC population would be beneficial; nevertheless there is some evidence that flying and anaesthesia may precipitate symptomatic LAM in some patients. It may therefore be prudent to undertake chest HRCT before an anaesthetic is administered in high risk patients. Screening before flying is more controversial and maybe should be discussed with each patient individually.

References

See appendix four.

CHAPTER EIGHT

Renal Disease

There were twenty-four patients with TSC in the Bath district; twenty-two underwent renal ultrasound scanning. Nearly two thirds (13/22) were found to have renal involvement and 13% (3/22) had been symptomatic. AML were most frequently found lesions, occurring in half of the patients screened. Five patients had cysts, one of whom had polycystic kidney disease. One patient was found to have a renal carcinoma. None of the rarer complications e.g. sarcoma were found in our group of patients.

Renal involvement is common in TSC with a wide diversity of renal disease most commonly angiomyolipoma (AML) and/or cysts with, more rarely adenocarcinoma, but oncocytomas, sarcomas, interstitial fibrosis and glomerulosclerosis have all been reported[34]. The severity of renal disease also varies widely. Many patients with AML with or without cysts will remain asymptomatic with normal renal function throughout their life, whilst others may suffer pain, haemorrhage, end stage renal failure (ESRF) and ultimately death from their lesions[29].

Three patients who were all known to have large bilateral AML experienced symptoms of pain and haematuria, requiring treatment with selective arterial embolisation. The patient with the renal carcinoma had been asymptomatic and the lesion discovered on routine scanning. The diagnosis was confirmed initially by CT scan and then by biopsy, the patient then underwent nephrectomy and is currently being followed up. None of our patients have died from their renal disease but renal complications are an important cause of premature mortality in patients with TSC. In the study carried out at the Mayo Clinic[32] looking at the cause of death in 40 patients with TSC, renal disease was the leading cause of mortality accounting for eleven of the deaths. Seven patients died of renal failure, two of renal carcinoma and two of haemorrhage from AML. The paper was not clear about the underlying pathology in the seven patients with renal failure.

End stage renal failure in adults with the tuberous sclerosis complex

To date no study has been carried out in the UK to look at the incidence or prevalence of ESRF in TSC or its clinical presentation and no paper has reported the underlying pathology in these patients. Therefore, the aim of this study was to examine both the prevalence and underlying causes of ESRF in patients with TSC.

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Method

This study was based on a questionnaire sent to the 170 UK members of the European Dialysis and Transplant Association in September 1993. The questionnaire asked if they currently had any patients with TSC in their renal replacement program. For those that did, the following clinical information was requested:

- Sex.
- Age of diagnosis of TSC.
- Age of diagnosis of renal disease.
- Age of onset of ESRF.
- The reason for diagnosis of TSC and whether the patient was a familial or sporadic case.
- They were also asked if the patient had ever suffered from epilepsy, learning difficulties, giant cell astrocytomas or pulmonary lymphangioleiomyomatosis.
- In addition, information was collected on the presenting features of the renal disease, including the presence or absence of hypertension, the underlying lesions, the confirmation of diagnosis and renal function at presentation.
- Finally, we asked about the treatment the patient received for their renal disease including the need for nephrectomy.

Results

Of the 170 members contacted, 142 (84%) replied with a total of ten patients being identified. At least one reply was received from each unit.

There were eight females and two males. The average age at diagnosis of TSC was 21.2 years (range <1 year to 34 years). Three patients had TSC diagnosed as a result of their renal disease (table twenty seven), the average age of diagnosis of TSC in these patients was 32 years compared to an average age of 16 .7 years in the other seven patients who

had TSC diagnosed on other criteria including skin lesions, epilepsy and family history (table twenty-seven). Six patients were known to be sporadic cases of TSC and two were known to be familial. Eight patients had a history of epilepsy and four had learning difficulties (one mildly) but none had a history of giant cell astrocytomas or pulmonary disease (table twenty-seven).

The average age of presentation of renal disease was 31 years (range 18 – 50 years). Only one patient (case 10) was known to have renal involvement prior to presentation of renal disease as a result of screening at the age of 18 months when he was diagnosed as having TSC. He had then remained asymptomatic until 26 years of age.

Table twenty-seven

	Sex	**Age TSC Diagnosed**	**Reason TSC Diagnosed**	**Familial / Sporadic**	**LD**
1	F	32 years	Family history	Familial	No
2	F	<1 year	Infantile spasms	Sporadic	Yes
3	F	About 12 years	Epilepsy	NK	No
4	F	29 years	Skin lesions	Familial	No
5	F	NK	Skin lesions	Sporadic	Yes
6	F	20 years	Skin lesions, Epilepsy	NK	No
7	F	34 years	NK	Sporadic	Yes
8	F	17 years	Renal Haemorrhage	Sporadic	No
9	M	5 years	Skin lesions, Epilepsy	Sporadic	No
10	M	18 months	Infantile spasms	Sporadic	Yes

LD = learning difficulty, NK = not known

Table showing the age and sex of the patients, the age at which TSC was diagnosed and the reason for diagnosis, whether the inheritance was sporadic or familial and the presence / absence of learning difficulties.

The presenting features varied widely (table twenty-eight). Seven had impaired renal function at the time of presentation, five had renal masses, four had raised blood pressure, three had haematuria, three complained of pain and one had a urinary tract infection.

Table twenty-eight

	Age at diagnosis of renal disease	Presentation	Age of ESRF (years)	Lesions	Diagnosis	Renal function at diagnosis	Hyper-tension at diagnosis
1	29 years	Renal masses	38	Carcinoma	Histology	NK	No
2	20 years	ESRF	20	NK	NK	ESRF	Yes
3	32 years	Renal failure	32	SK and cysts	USS	NK	Yes
4	32 years	Haematuria	48	AML and cysts	IVP	Normal	No
5	44 years	Acute on chronic renal failure	49	PKD	USS	ARF	No
6	26 years	Pain Renal masses	26	SK and cysts	USS	CRF	Yes
7	34 years	Pain, renal masses and haematuria	40	PKD	CT	CRF	Yes
8	18 years	Acute abdomen	19	AML	CT Histology	Normal	No
9	50 years	UTI Renal masses	55	PKD	USS	CRF	No
10	26 years	Pain Haematuria	26	PKD	USS	ESRF	Yes

ESRF = end stage renal failure, UTI = urinary tract infection, NK = not known, Cr = creatinine, SK = small kidneys, USS = ultrasound scan, PKD = polycystic kidney disease, CT = CT scan, CRF = Chronic renal failure (all had high creatinine at presentation).

Table showing the age of presentation of renal disease and age of ESRF, presentation of renal disease, the underlying lesions, method of confirmation of the diagnosis, renal function at time of presentation of renal disease and the presence / absence of hypertension.

There was a range of underlying pathology; four patients were noted to have PKD, one patient had AMLs and cysts, two were noted to have small kidneys with cysts and one

patient had AML alone, one patient had bilateral adenocarcinoma and in one patient the underlying pathology was not clear (table twenty-eight). The underlying pathology was confirmed by ultrasound in five patients, CT scan in one, CT and histology in one, histology alone in one and one by intravenous pyelogram (IVP): in one patient it was not clear how the diagnosis had been confirmed (table twenty-eight). The average age of end stage renal failure was 35.3 years.

Nephrectomy had been performed in four patients. Two patients had undergone nephrectomy (one bilaterally) for carcinoma, one because of haemorrhage, and the fourth patient had surgery for symptomatic relief. Nine patients had dialysis, haemodialysis in five, peritoneal haemodialysis in three and a combination in one. Seven patients had a renal transplant, one without prior dialysis of which five were successful (table twenty-nine).

Table twenty-nine

	Reason for Nephrectomy (if performed)	**Treatment**
1	Bilateral Adenocarcinoma (bilateral nephrectomy)	Transplant
2		Haemodialysis Transplant
3		2 x failed transplant Haemodialysis
4	Adenocarcinoma	Haemodialysis Transplant
5		Haemodialysis Transplant
6		Failed transplant Peritoneal dialysis
7	Symptomatic relief	Haemodialysis
8	Haemorrhage	Haemodialysis Failed transplant Peritoneal dialysis Successful transplant
9		Peritoneal dialysis
10		Peritoneal dialysis

Table showing the treatment of ESRF in the patients in our survey.

Discussion

The prevalence of TSC is 1:23,000 between 15 – 45 years and 1: 97,000 over 45 years: we would therefore expect 1,350 adults in the UK to have TSC of whom approximately half will have normal intelligence. It is possible that in the UK patients with intellectual disability (i.e. half of patients with TSC) are less frequently referred to a renal replacement program. We have identified 10 adults, six with normal intellect who have end stage renal failure and TSC in the UK giving a prevalence of 1% in those with normal intellect. There are other possible inaccuracies. Firstly, the response rate to our questionnaire was only 84% and it is conceivable that there are patients with TSC who were not notified. It is also likely that some patients with ESRF due to TSC are not recognised because either they do not exhibit other overt signs of TSC or are only mildly affected. However recent analyses suggest the prevalence of TSC[1] may be higher than previously recognised which would reduce the risk of ESRF in TSC. The approximate risk of ESRF in TSC may be different in those with learning difficulties – recent studies have begun to suggest that TSC2 gene defects may produce a more severe phenotype than TSC1 disease at least as far as intellect and epilepsy is concerned with no data yet on renal disease, other than PKD. A study carried out in France[42], making different presumptions, also found the prevalence of ESRF in adults with TSC to be 1 in 100. They do not state if this is the whole of the adult population with TSC or those with normal intellect only. No mention is made of the underlying causes.

In our survey there was a preponderance of females. A study carried out by Webb[159] et al suggested asymptomatic renal involvement to be as common in males as females. The small numbers might account for this discrepancy, but it might reflect that females tend to have more severe disease than males. It is well documented in the literature that females have a higher probability of symptoms from the lung complications of TSC (lymphangioleiomyomatosis – see chapter seven) than males. One explanation is that female hormones play a part in influencing the disease. This theory has been backed up by the finding of hormone receptors[150] in affected lungs and that the course of the disease may be affected in some patients by hormonal manipulation (e.g. oophrectomy) or by natural changes in hormone levels (e.g. pregnancy[132] and menopause[134]). It is therefore feasible that oestrogens and progesterone similarly influence the renal lesions as the lung lesions. The underlying histopathology is similar for most TSC lesions in that they arise as

hamartomas from over proliferation of otherwise normal tissue as a result of inactivation of tumour suppressor genes.

Inheritance of TSC is autosomal dominant with a spontaneous mutation rate of about 60%. Only two patients in our survey had parents with TSC, six were known to be sporadic mutations and in two the mode of inheritance unknown.

The patients in our survey represented a wide spectrum of renal disease seen in TSC. As discussed before, the TSC2 gene is close to the PKD1 gene, but PKD1 mutations do not underlie the cytogenesis in all patients. Renal disease including cysts occurs in patients with both TSC1 and TSC2. Although polycystic disease was more common in our survey of TSC patients with renal failure than is found in the TSC population, PKD was the cause of ESRF in only four of our patients; PKD is a known cause of ESRF, it is to be expected that this cause would be significantly represented in our survey, the pathological causes of ESRF in the other patients are more interesting.

The underlying pathology probably contributes to the renal failure by a variety of mechanisms. There may be compression of the normal renal parenchyma by cysts, angiomyolipoma or carcinoma. There may be a reduction in the amount of normal tissue either as a result of direct invasion by tumour or resulting from surgery. In addition it has been hypothesised that cysts in particular cause hyperfiltration of the remaining glomeruli, creating focal glomerulosclerosis[42].

Probably as a reflection of the range of underlying pathology our patients presented in many different ways from simple haematuria to massive intra-abdominal haemorrhage; from acute renal failure to insidious chronic renal failure. They all presented in adulthood with a mean age of 31 years progressing to ESRF at an average of 35.3 years.

Confirmation of renal disease was made by ultrasound in the majority of cases. Ultrasonography is particularly sensitive in detecting cysts and intramural or perinephric haemorrhage[160], but the echodense pattern seen on ultrasound although suggestive of AML is not pathognomonic. Renal carcinoma tends to be echolucent on ultrasound. CT is highly specific for AML when fatty tissue can be demonstrated within the lesion[161]. If any doubt remains biopsy can be undertaken to exclude malignancy, but it can give very misleading

results. Histology at the edge of AML may look like renal carcinoma but recent studies suggest that staining for HMB45, which is positive in AML and negative in carcinoma, can differentiate it[162]. CT has the disadvantage of radiation and the theoretical risk of inducing further hamartomas, but while MRI can demonstrate renal lesions it does not demonstrate fatty tissue well.

Treatment of the renal lesions may contribute to the development of ESRF as discussed above. Nephrectomy remains the treatment of choice for patients with carcinoma, but transcatheter embolisation of distal branches of the renal artery for haemorrhage or pain offers a more conservative form of treatment allowing greater preservation of parenchymal tissue, thereby either delaying or preventing the onset of ESRF. Once ESRF has occurred treatment consists of dialysis and transplantation. There is still controversy as to whether nephrectomy should or should not be performed in patients undergoing transplant. Advocates argue that the diseased kidney carries a risk of bleeding and malignancy and should therefore be removed at the time of transplantation. Others argue that the disease free part of the kidney may retain some function which will be of use to the patient should rejection of the transplanted kidney occur.

Screening for renal disease in patients with TSC also remains controversial (please see chapter seven for the criteria for a good screening programme).

Presymptomatic diagnosis of PKD is known to be advantageous, for control of hypertension, prompt treatment of urine infections, close monitoring of renal function and early treatment of renal bone disease, but other lesions are much more common. Unlike LAM a suitable screening tool is available; ultrasound can be used to detect PKD in the young infant. Ultrasound scanning is a safe non-invasive technique which is generally acceptable to patients and parents. It is generally accepted that once a diagnosis of TSC has been made in an infant or young child that a renal USS should be undertaken to allow diagnosis of associated PKD. However, for the other lesions seen in TSC many of the criteria for good screening discussed in the previous chapter can not be met.

Studies in the past have suggested that AML, which bleed, are likely to be greater than 3.5 – 4cm in diameter[163]. Some would therefore advocate screening for AML so that when they reach such a size prophylactic treatment could be undertaken. Ultrasound can be used

to detect small AML and to monitor their size. However, the natural history of progression from latent to established disease remains unclear; size is not always predictive of haemorrhage and some individuals with longstanding large AML have never suffered haemorrhage. It might be the rate of expansion or some other factor which causes haemorrhage; and whilst treatment (embolisation and / or surgery) is available it is not without risk and complications, for example pain, infection, loss of normal renal tissue and risk of embolisation elsewhere; neither is screening, for example it can force people to know they have a disease, and may highlight the presence of disease other than that for which they undertook screening[164]. Neither is it known that embolisation is curative. Others would therefore wait until the lesions become symptomatic before initiating treatment.

Likewise, screening for ESRF is not currently undertaken in the TSC population. At present there is no screening test available that is simple, easy to interpret and acceptable to the patients. In order to detect very early ESRF it is likely that regular renal function testing involving venesection and blood pressure monitoring would be required. Whilst the measurement of blood pressure in simple and non-invasive and should be routinely performed as good clinical practice, many patients are not keen to have venesection performed. In addition, at present it is not known how frequently renal function would need to be undertaken to detect a decline in renal function before the onset of ESRF, nor whether treatment will help. Further research is required to understand the natural history and other factors to determine the risks and benefits of screening in these patients.

Conclusion

ESRF is rare in patients with TSC but does contribute significantly to the premature mortality in this group. At present there are no clear prognostic factors that can be used to determine which individuals are at greatest risk of developing ESRF, other than it appears to be more common in females. Importantly it may be possible to delay, or even prevent renal failure in some patients by undertaking more conservative forms of management, such as embolisation rather than nephrectomy in the earlier stages of disease.

CHAPTER NINE

Sleep Disorder In Tuberous Sclerosis Complex

Over the past decade, sleep disorder in TSC has become increasingly recognised as a frequent cause of morbidity and stress not only for the patients suffering from TSC, but also for the families caring for them. In 1993 Hunt[165] undertook a postal survey of 300 TSC patients; carers reported problems with settling in 60% and night waking in 62% of children with TSC. In an earlier study Quine and Pahl[166] found that the sleep disorder experienced by children with neurological disabilities was one of the greatest contributing factors to stress experienced by the families of such patients.

Normal sleep patterns
Sleep can be defined as a state of altered or reduced consciousness from which a person can be aroused by appropriate sensory or other stimuli. During a normal nights sleep a person goes through two main types of sleep that alternate with each other; slow wave and rapid eye movement (REM) sleep. Slow wave sleep accounts for about three quarters of the total sleep time and is called so because the frequency of the EEG becomes progressively slower until it reaches a frequency of 2-3 waves a second (delta waves). This type of sleep is further divided into four phases. Stage one occurs when the person is initially falling asleep and the EEG shows low voltage waves interspersed with sleep spindles (short bursts of high frequency, high voltage activity on the EEG), in stage two the sleep spindles disappear and in the following stages the background EEG frequency gradually decreases. REM sleep occurs through out the night in a cyclical fashion and is associated with dreaming. It is thought that not only are both slow wave and REM sleep necessary for a restful nights sleep but also the cyclical alternation between the two.

In 1994 Hunt and Stores[27] undertook a further questionnaire-based study looking at sleep disorder (and its relationship to epilepsy) in TSC in greater detail. This study looked at forty children with TSC (identified via the Tuberous Sclerosis Association (GB)); a sample representing 5% of the estimated total population of the children with TSC in the UK aged between two and fifteen years. They used two groups of non-disabled children as controls; the first group contained 22 siblings of the TSC group (aged three to seventeen years) and the second group 37 children attending mainstream school (who were each matched for gender and age with a child in the TSC group). The three pre-school aged children in the TSC group did not have matched controls.

Sleep disturbance was calculated using the Quine Sleep Index score[167], which looks at the four following areas in sleep disturbance:

1. Difficulties settling the child to sleep.
2. Night time wakening.
3. Parents /carers attendance to the child during the night.

4. Parental sleep loss.

Each area is scored on a three point score (0 –2) dependant on the severity and frequency of each problem giving a total score 0 - 8.

They found the degree of sleep disruption in their group of children with TSC to be significantly greater ($p < 0.001$) than in the 22 siblings and 37 matched controls. The mean sleep index for children with TSC was 4.9 (SD 3.1), compared with 0.59 (SD 1.02) for the siblings and 0.41 (SD 0.68) for the matched controls, thus confirming that settling and night time waking was more common in children with TSC than either their siblings or other children attending mainstream school. Hunt and Stores do not state clearly how the study subjects were recruited and it is possible that their group of children with TSC represent the 5% with the greatest sleep difficulties and that the controls were chosen because they were known not to have any sleep disturbances. Nevertheless, this study does suggest that some children with TSC do suffer significant sleep disturbances.

Hunt and Stores also looked at the associations of sleep disturbance with epilepsy and behavioural problems. Behaviour was rated using the Developmentally Delayed Children's Checklist (Einfeild and Tonge 1991), constructed specifically to include the most prevalent behaviours observed in children with learning difficulties. Again they found the scores for the children with TSC to be significantly higher ($p < 0.001$) than those without. The children with TSC were further divided into two groups; those with current seizures and those who had either been fit free for the six months preceding the study or who had never had seizures. The mean Sleep Index of the former group was 6.24 (SD 2.44), and significantly higher than the mean 1.45 (SD 1.50) for the latter group ($p < 0.001$).

Seizures are known to disrupt sleep patterns in many ways including[168];

- fragmentation by frequent awakenings,
- reduced REM sleep,
- increase in wakefulness after sleep onset,
- instability of sleep stages.

The sleep disorder in TSC is more complex than this with other multiple contributory factors since the following are also known to affect sleep and occur in many patients with TSC;

- autism,
- hyperactivity,
- learning difficulties which in turn may affect the development of normal behavioural zeitgebers (e.g. bed time routines which can be powerful enough to enforce the natural circadian rhythms of melatonin secretion in the absence of light-dark cycles),
- anticonvulsant medications; often prescribed in patients with TSC may affect sleep.

Sedatives often prescribed for children with sleep disorders are generally ineffective and clinical experience suggests that in children with TSC they are even less likely to be effective. In fact they often worsen the situation by increasing hyperactivity. Behavioural techniques are also of less benefit to many of these patients, because of the above contributory factors and because of the extreme exhaustion of caring for these children day and night.

Normal sleep-wake cycles
The underlying physiological process for normal sleep-wake cycles in not yet fully understood and is likely to be complex, involving the circadian secretion of neurotransmitters and learnt behavioural patterns (zeitgebers). Early theories suggested that the reticular activating system and other parts of the brain became 'fatigued' over the period of a waking day and therefore became inactive resulting in sleep. It was then thought that the raphe nuclei (situated in the brainstem), which produces serotonin, a neurotransmitter known to induce sleep was responsible. However, serotonin does not appear to be secreted in a circadian manner. It is now thought that Melatonin, a hormone secreted from the pineal gland plays a major role in the normal sleep-wake cycles. Melatonin is thought to synchronise sleep-wake patterns with the light-dark cycle of the normal day, through pathways from the retina, via the hypothalamus, to the pineal gland. Decreased light intensity at the retina (i.e. darkness) leads to an increase in melatonin production, which in turn leads to drowsiness.

With the advancing interest in the treatment of sleep disorders in children, melatonin has become one of the forerunners as a potential therapy for disruptive sleep patterns. Melatonin was first used in its synthetic form in 1981 by Weitzman[169] et al to regulate sleep patterns in shift workers. It was then shown to be successful in alleviating jet-lag in adults by Arendt et al[170]. First to show success in treating the sleep disorders of disabled children (both with and without visual impairment) were Jan et al[171] in 1994.

A study of nine girls with Retts syndrome[172] (but no visual impairment) was then undertaken by McArthur et al 1998. Wrist actigraphs and sleep diaries were used to monitor the sleep patterns of the nine patients. There was a one-week baseline period followed by a double blind, placebo controlled, crossover trial lasting eight weeks with a one-week washout period between the two crossover periods. The dose of melatonin given

was based on weight and ranged from 2.5mg to 7.5mg. Sleep-onset latency was significantly reduced by melatonin, reducing from 32 +/- 8.6 minutes during the placebo period to 19.1 +/- 5.3 minutes ($p = 0.05$) with melatonin treatment. They also found that melatonin increased the total sleep time in some patients but that this did not reach clinical significance. Melatonin did not alter the frequency of night-time awakenings in this group. Their group experienced no adverse effects.

The results of these studies led our group to assess the use of melatonin patients with TSC and sleep disorder[173]. A randomised double blind, placebo-controlled crossover study comparing 5mg melatonin (regardless of weight) against placebo was carried out in seven patients with confirmed diagnoses of TSC and significant associated sleep disorders. There were three males and four females and the age range was two to twenty-two years (median eleven years). All the patients were epileptic and had learning difficulties. Three outcome measures were applied; total sleep time, time to sleep onset and number of awakenings. Patients when treated with melatonin had a significant improvement in total sleep time (mean improvement 0.55 hours, $p < 0.05$), and tended to have an improvement in sleep onset time, which was not significant. There was no significant decrease in sleep fragmentation. Although the improvement was modest it was of great significance to the carers; half an hour over seven nights is an extra three and half hours extra sleep a week.

However, there were still unanswered questions. Firstly, there was the question of optimum dosage, Jan et al[171] used a dose of 2.5 – 10mg in their study and McArthur et al[172] a dose of 2.5 – 7.5mg in their study, both with promising results. However, another study by Camfield et al[174] had used smaller doses of 0.5 –1mg with less benefit. It might be possible that the effect is dose related. Secondly, the mechanism by which melatonin improves sleep patterns in these patients remains unclear. There are many complex factors, which contribute to the normal wake-sleep patterns, and the relationship between melatonin production and onset of sleep is not a simple one. For example, populations living in Northern Europe and the Artics do not sleep throughout the winter months where there is darkness all of the day, and we all feel tired as the evening progresses despite the fact that our homes are lit by electricity. There are therefore other factors, including learned behavioural routines (zeitgebers) that also contribute to the normal wake-sleep cycles. It is possible that TSC patients, with learning and behavioural difficulties, do not

acquire these normal social responses that aid the sleep-wake cycles. It is also possible that TSC patients may not have a normal pattern of melatonin secretion.

The Effect of Melatonin Dosage on the Sleep Disorder in Tuberous Sclerosis Complex

Aim

The aim of this study was to investigate whether there is a dose related response to exogenous melatonin when using a dose higher than 5mg in patients suffering sleep disorder associated with TSC.

Methods

Ethical approval for the study was obtained from the Bath Local Research Ethics Committee. Patients with a confirmed diagnosis of TSC and severe sleep problems were then identified through the Bath TSC clinic, research and epidemiological studies. A diagnosis of TSC was confirmed by the presence of at least one hamartoma present in each of a minimum of two different organs. A diagnosis of sleep disorder was confirmed by a Quine sleep index score of at least six out of a possible eight[167]. The Quine index focuses on four areas of sleep difficulties; difficulties settling the child to sleep, night time wakening, parents /carers attendance to the child during the night and parental sleep loss. Children were excluded from the trial if their sleep disorder proved to be situational (for example a child that scored six on the Quine questionnaire whilst at home, but two whilst at respite care would not be included in the trial).

This was a randomised double-blind controlled crossover trial comparing 5mg and 10mg of melatonin. Melatonin was supplied by Penn Pharmaceuticals Ltd. Melatonin 5mg and placebo (a sugar compound) were administered in identical capsules. The trial consisted of four parts; an initial two week baseline period during which the patients received no treatment, a two week period during which the patient received either 5mg or 10mg of melatonin, a two week wash-out period during which the patient received no treatment and a two week period during which the patient received the alternate dose of melatonin (i.e.

5mg or 10mg). The parents / carers completed both sleep and seizure diaries (see appendix five) throughout to document the sleep disorder and seizure frequency.

Melatonin was administered approximately thirty minutes before the patients' usual bedtime; each patient received two identical capsules, either 2 x 5mg of melatonin (i.e. 10mg in total) or 1 x 5mg plus 1 x placebo (i.e. 5mg in total). The patients, carers and researchers did not know which weeks they received 10mg of melatonin and which weeks they received 5mg of melatonin.

The sleep diaries were used to monitor the sleep latency (i.e. time taken to fall asleep), the total sleep time and the number of awakenings each night. The seizure diaries were used to monitor the frequency and type of seizures (if any) experienced by the patients during the study period. The carers were also asked to record any illnesses the child had or any possible side effects they suffered during the trial period.

Results were analysed using paired t-tests.

Results

Eight patients were recruited who satisfied the inclusion criteria. One patient completed the study but the diaries were lost in the post and we had not thought to ask to have them photocopied before they were posted to us. We present the results of the seven whose diaries are available. There were four males and three females with an age range of 18 months to 31 years (median age 9 years). All patients were epileptic and on concurrent anticonvulsants, two of whom were well controlled. All had severe learning and behavioural difficulties.

The results are shown in table thirty and although there was a small improvement in sleep latency time in the 10mg group compared to the 5 mg group, it does not reach conventional levels of statistical significance ($p = 0.4$). Total sleep time was calculated for each of the seven patients during each two-week phase of the trial. There was no statistical significance between the two groups ($p = 0.6$). The mean number of awakenings was recorded for five of the patients, but was not recorded by the carers in the other two patients, again there was no statistical difference between the two groups in terms of sleep fragmentation ($p = 0.5$).

Table Thirty

Patient	Age	Sleep latency 5mg	Sleep latency 10mg	Total sleep time 5mg	Total sleep time 10mg	Fragmentation 5mg	Fragmentation 10mg
1 female	18 months	154 mins	105 mins	8 hours 51 mins	9 hours 25 mins	0.9	2.5
2 female	4 years	102 mins	128 mins	9 hours	7 hours 47 mins	0.9	1.0
3 female	9 years	53 mins	50 mins	8 hours 54 mins	8 hours 39 mins	0.2	.2
4 male	9 years	30 mins	46 mins	9 hours 28 mins	10 hours 29 mins	0.6	.2
5 male	11 years	11 mins	13 mins	9 hours 30 mins	9 hours 20 mins	1.2	1.2
6 male	19 years	208 mins	154 mins	8 hours	9 hours 36 mins		
7 male	31 years	46 mins	36 mins	8 hours 55 mins	8 hours 38 mins		
Mean		86 mins	76 mins	8 hours 57 mins	9 hours 4 mins	0.8	1.0

Table showing the mean sleep latency, total sleep time and sleep fragmentation after the administration of 5mg melatonin and10 mg melatonin.

In the five patients who had seizures during the trial, the seizure diary showed no change in the frequency (or type) of seizures seen compared to the initial baseline period before melatonin treatment. Three patients were well controlled on their anticonvulsants and remained seizure free during the study (table thirty-one).

There were no adverse side effects reported by the carers during the trial period.

Table thirty-one

Patient	Age	No. of seizures without melatonin	No. seizures on 5mg melatonin	No. of seizures on 10mg melatonin
1 (f)	18 M	None	None	None
2 (f)	4 Y	23 / week	20 /week	20 / week
3 (f)	9 Y	None	None	None
4 (m)	9 Y	4 / week	3 / week	3 / week
5 (m)	11 Y	5 / week	6 / week	6 / week
6 (m)	19 Y	None	None	None
7 (m)	31 Y	73 / week	159 / week	40 / week
			p = 0.38	p = 0.31

Table showing seizure frequency; without melatonin; after the administration of 5mg melatonin; and after the administration of 10mg melatonin.

Discussion

The best way to accurately monitor sleep and its disturbance is by polysomnography; this was not possible in our group of patients. We chose to use sleep diaries, which is an inexpensive method of monitoring sleep patterns. Although, reliant on the vigilance of already overburdened caregivers, they demonstrate symptoms and any bias in minimised by the double blind nature of the study. McArthur et al used wrist actigraphs in their study[172] and found them to be more accurate than sleep dairies but they too have disadvantages; they are prone to mechanical failure and non-compliance, which may lead

to total loss of data. The effect of nocturnal seizures on actigraphs is a further complication in patients with TSC since the assumption is that movement is an awakening when it might be due to a seizure.

Although only a few studies have been undertaken looking at the effect of melatonin on sleep disturbance in children with severe neurological difficulties with mixed results, the combined results suggest that the effect seen might be dose related. Studies using higher doses (2.5mg – 10mg) demonstrated a response while those using lower doses (0.5mg – 1.0mg) did not.

The results from our previous study[173] comparing the effects of 5mg of melatonin versus placebo, found increased total sleep time and a trend towards decreased sleep latency, but with varying responses between subjects. We also found a trend towards increased total sleep time and decreased sleep latency when comparing our baseline data (i.e. no melatonin) with administration of 5mg melatonin; however we have not reported these findings since they were not blinded and are therefore prone to attrition bias. We have shown that the administration of 10 mg of melatonin did not further reduce the sleep latency, improve the total sleep time or reduce sleep fragmentation in our group compared with 5mg. One possible explanation for this lack of dose related response is that 5mg is already a supraphysiological dose.

The exact mechanism by which melatonin improves sleep patterns in these patients remains unclear, many hypothesis have been suggested; the simplest that melatonin has a straight forward sedative effect. This would explain the clinical effect seen in our patients i.e. reduced sleep latency. It is also known that melatonin is metabolised rapidly and that there is a large hepatic, first pass metabolism so that, in humans, peak plasma levels are reached within one hour and there is a half life of approximately 45 minutes (personal communication). This rapid metabolism may explain why total sleep time and sleep fragmentation remained unimproved.

Another hypothesis is a link with epilepsy. All our patients were known to suffer from seizures and were on concurrent anticonvulsants during the trial. It is known that epilepsy plays an important role in the sleep disturbance of TSC[175] by disrupting the normal sleep physiology in a variety of ways. It has also been suggested that melatonin may influence

epileptic activity in humans, though the exact relationship remains unclear. In 1974[176] melatonin was reported to improve seizure control in epileptic subjects, an observation also noted in mice[177] when used in large doses (i.e. >200mg/kg). In 1985[178] Maurizi showed melatonin to increase levels of serotonin in the brain thus raising the seizure threshold. In 1994 Molina et al[179] and in 1995 Schapel[180] both demonstrated that patients with epilepsy had higher serum concentrations of melatonin than individuals without epilepsy suggesting the possibility of a physiological attempt to reduce seizure threshold in these patients. Only Sheldon et al[181] have suggested in an observational study reported in a letter to the Lancet that oral administration of melatonin in disabled children might paradoxically result in an increase in seizure frequency.

All our carers completed seizure dairies for the eight-week duration of the sleep trial. There appeared to be no significant effect of melatonin administration on seizure activity in any of our patients.

It is also possible that some patients with TSC have either abnormally low or disrupted melatonin secretion. Although previous authors[180] have suggested that patients with uncontrolled epilepsy have increased nocturnal melatonin production, others have suggested that the circadian rhythm is disrupted with peak levels occurring earlier in the night than normal subjects[179]. However, to our knowledge, no one has looked at the circadian rhythms of melatonin production in children and comparisons have been made against adult data. In addition no study has looked at melatonin production in patients with TSC and epilepsy. We have addressed this in a separate study.

This study did not find any detrimental effect on seizures. However, there were only seven patients and it is possible that we have insufficient power to detect a significant difference in response, or that individual patients might benefit from a higher dose. Since none of our patients reported any adverse effects whilst taking the melatonin, we would suggest when treating this group of children for sleep disorder that 5mg melatonin is used and 10mg is only considered if 5mg fails to be of any benefit. Further studies on the use of melatonin would be worthwhile – looking further at dosage and tolerance over a prolonged treatment period.

None of our patients reported any adverse effects whilst taking the melatonin.

Conclusion

In conclusion, whilst it seems likely that the administration of exogenous melatonin in patients with TSC and sleep disorder does reduce sleep latency and increase total sleep time, higher doses show no further benefit. The response to melatonin does seem to vary between individuals and we would propose that a trial of 5mg of melatonin given 30 minutes before bedtime is worth considering in these patients and that the response should be monitored by both sleep and seizure diaries. If no beneficial response is seen within two weeks then, while there is no proven advantage in increasing the dose of melatonin to 10mg, this is unlikely to cause significant side effects if it is considered. More studies are required.

Melatonin excretion in normal children and tuberous sclerosis with sleep disorder responsive to melatonin

Trials have established the beneficial effects of exogenous melatonin in the treatment of sleep disorders in children, but the mechanism of action remains unclear. It has been postulated that some children might have aberrant endogenous melatonin secretion that can be corrected by giving exogenous melatonin.

Melatonin is excreted in the urine as 6-sulphatoxymelatonin (a relatively stable metabolite) that can be easily measured. The pineal output of melatonin is believed to be very stable from day to day so it is not necessary to collect urine over long periods of time. Total excretion, the time of maximal excretion (acrophase time) and the wave form of excretion over 24 hours (cosinor rhythm) can all be measured. A cosinor rhythm of less than 70% can be due to inaccurate collection while if over 90% an accurate collection with normal circadian rhythm can be inferred.

Aims

The aims of this study were firstly to measure the melatonin excretion in six children and one adult suffering from sleep disorder responsive to melatonin (all these patients also suffer from TSC) and secondly to measure melatonin excretion in healthy children to obtain normal excretion data for age. The Bath Local Research Ethics Committee granted ethical approval.

Methods

Six children and one adult suffering from sleep disorder and TSC were recruited for the study. All seven subsequently took part in a study comparing the effect of 5mg melatonin versus placebo and were shown to have a significant improvement in total sleep time and a tendency to decreased sleep latency when treated with melatonin[173]. We also recruited 21 healthy children (between the ages of 5 and 15 years) who had no sleep problems. There were two for each year of age, except for five years, where we were only able to recruit one because of difficulties with compliance. We asked them to collect their urine over a 48-hour period in four hourly aliquots. The children were not woken in the night in order to collect samples, but if they woke naturally to pass urine then a specimen was taken. They were asked to pass urine, discard that first sample, note the time and then start the 48-hour collection, collecting at least one sample four-hourly whenever possible. Each time they subsequently passed urine they would note the time and the quantity passed. The specimens were then frozen until the time of analysis.

All specimens were sent to Stockgrand Ltd, affiliated to the School of Biological Sciences at the University of Surrey for analysis. Melatonin excretion was expressed as the total 6-sulphatoxymelatonin secretion, cosinor analysis and the acrophase time over each of the two consecutive 24-hour periods.

The results from the first 24-hours excretion of each healthy child were then analysed, both including and excluding any results with a cosinor analysis of less than 70% and were then compared with the second 24-hour excretion period to give an estimate of the repeatability of the results. Only the excretion data from the first 24-hour period were used to determine normal excretion.

The excretion data obtained from the patient group was then compared with the data obtained from the healthy children and normal adult data.

Results

Tables thirty-two and thirty-three show the total daily excretion of 6-sulphatoxymelatonin, the cosinor rhythm and the acrophase time for the healthy children and the patients

respectively. For each individual, two results are given, one for each of the 24 hours of the 48-hour collection. There were no significant differences or trends seen with age.

Table thirty-two

Controls (age years)	Total 6SM (nanograms)	Cosinor %	Acrophase Time
5	11,112	99.9	02.30
	12,505	96.4	04.00
6	40,175	75.0	03.24
	30,574	99.7	03.48
6	17,148	99.1	01.36
	12,715	100.0	04.42
7	28,971	94.9	04.42
	28,374	96.2	05.00
7	24,386	57.8	08.30
	21,687	76.5	07.24
8	21,474	68.9	23.54
	16,167	73.6	01.54
8	28,820	95.7	02.12
	33,055	92.7	01.00
9	14,778	74.8	08.12
	14,630	81.1	09.42
9	11,911	94.9	03.06
	11,510	100.0	04.24
10	20,220	93.2	06.36
	20,529	56.9	09.42
10	11,184	92.7	04.00
	10,110	100.0	05.18
11	17,583	99.4	03.06
	21,074	96.9	04.48
11B	15,175	83.5	10.42
	9,368	82.8	09.24
12	21,690	52.9	07.36
	18,644	100.0	03.36
12	16,820	99.9	05.42
	18,753	98.4	05.48
13	11,266	96.8	04.12
	11,915	100.0	05.36
13B	15,201	61.0	07.54
	13,209	75.4	09.42
14	24,785	97.7	05.18
	25,020	99.4	05.18
14	19,528	93.4	03.30
	18,020	99.0	05.00
15	10,760	99.3	03.36
	11,850	98.9	05.06
15	15,808	100.0	03.24
	16,307	96.9	02.24

Table showing the total 6-sulphatoxymelatonin excretion, the cosinor rhythms and acrophase times for the healthy controls. The first 24 hour excretion is given above the second 24 hour excretion for each child.

In the healthy children total daily excretion of 6-sulphatoxymelatonin in the first 24 hours ranged from 11,112 to 40,175 nanograms with a mean 18,991 nanograms (SD 7,384) and a median 17,148 nanograms. The cosinor rhythm ranged from 52.9% to 100%, with a mean of 87% (SD 15.5%) and a median of 94%. The acrophase time varied from 23.54 to 10.42 with a mean of 05.54 (SD 04.48) and a median of 04.12.

From the healthy children, we then excluded the results with a cosinor rhythm of less than 70%. Total daily excretion of 6-sulphatoxymelatonin ranged from 11,911 to 20,220 nanograms with a mean of 18,591 nanograms (SD 8,027 nanograms) and a median of 16,820. The acrophase time ranged from 03.06 to 05.18 with a mean of 04.30 (SD 02.20) and a median of 03.36.

Table thirty-three

Patients No. (age years)	Total 6SM (nanograms)	Cosinor %	Acrophase Time
1	13,100	95.9	02.00
(6)	13,100	69.1	23.24
2	13,500	98.6	02.36
(5)	11,500	96.8	01.18
3	600	51.9	10.36
(11)	1,200	93.2	02.36
4	40,500	97.9	02.48
(6)	45,800	93.7	01.54
5	26,600	93.2	04.30
(8)	30,800	93.8	04.48
6	32,300	67.8	05.24
(14)	32,300	69.0	05.36
Normal range for healthy controls (5^{th}-95^{th}%)	**11,112–28,971**	**57.8-99.9**	**02.12-10.42**
7	8,000	99.5	05.36
(28)	8,500	97.9	04.30
Normal range for adults[12]	**2,000-30,000**	**>90%**	**Early morning**

Table showing the total 6-sulphatoxymelatonin excretion, the cosinor rhythms and acrophase times for the TSC patients.

n the healthy children samples for 6-sulphatoxymelatonin and cosinor rhythm from the second 24 hours all fell above the 5^{th} centile (11,112 nanograms and 57.8% respectively). The acrophase times all fell within the 5^{th} and 95^{th} centile (02.12 and 10.42) except for one that was at 01.00.

In our group of patients with tuberous sclerosis and sleep disorder, there were six children and one adult. In the children, the total 6-sulphatoxymelatonin fell below the 5th centile in one patient and above the 95th centile in one patient. The cosinor rhythm fell below the 5th centile in one patient and the acrophase time fell before the 5th centile in three patients. The adult patient showed excretion within the normal range for adults[182].

Discussion

For our healthy controls, we chose five years as the lower limit, as we anticipated that children below this age would be too young to co-operate. We took 15 years as the upper limit as we felt that by 16 years excretion rates were likely to be similar to adult excretion rates. We found no significant differences with age, although the very youngest children tended to have slightly earlier acrophase time – perhaps because they go to bed earlier. This finding is compatible with the results of Sivan[184] et al who found a very early acrophase time in normal infants. Adult data shows total daily excretion to be 2,000 to 30,000 nanograms, with a cosinor rhythm of >90% and an acrophase time within the early hours of the morning[183]. Our data is compatible with this and with the data of Sivan[183] et al suggesting that melatonin excretion is in a recognisable circadian rhythm from an early age. This is also compatible with the data of Attanasio et al[184] who showed a circadian rhythm to melatonin excretion by measuring serum melatonin levels from infancy to adolescence.

Melatonin excretion is not thought to vary greatly from day to day, but we chose to collect our samples over two days to not only help assess how accurate the collections were, but also to assess repeatability. Although a cosinor rhythm of 90% infers accurate collection, it is also dependant on having a circadian rhythm. Our hypothesis was that patients with sleep disorders might not have normal circadian rhythms as shown by a low (less than 70%) cosinor value, therefore we could not rely on this value alone. We therefore also examined total 6- sulphatoxymelatonin excretion. Where the values from both 24-hour collections were similar it suggests that all the urine passed in the 48-hour period was measured and collected and no urine samples were "missed". For example, it is possible that the second eleven year old failed to collect at least some urine, perhaps on both days, accounting for the low melatonin excretion and cosinor rhythms. A high cosinor value correlates with a good circadian rhythm, however it was felt that ethically it was not acceptable to wake the children in the middle of the night to ask them to pass urine, but

only to collect the urine if they woke naturally. Failing to collect the urine at frequent intervals risks smoothing out the cosinor curve of a circadian rhythm and this might explain why some of our children had low values. We also had to rely on the family to correctly time and label the specimens, and any failures will have affected acrophase time and cosinor rhythm. However, such failures will also occur in clinical practice, and contribute to the "normal" range.

All our patients except patient three had 6-suphatoxymelatonin values that fell within the normal range. Interestingly, patient three, as an individual also had a poor response to exogenous melatonin. The fact that she did not respond to a "supraphysiological" dose of melatonin strengthens the hypothesis that exogenous melatonin does not act by correcting abnormal excretion patterns. This patient also had severe behavioural problems and this may explain in part, her poor sleep patterns and poor response to melatonin. All but one of the patients with TSC and sleep disorder had at least one cosinor value above 90% indicating strong circadian rhythms. The one who did not, had responded to melatonin as an individual with an improvement in total sleep time. The acrophase time is indicative of the time at which maximal melatonin excretion occurs. In adults this occurs in the early hours of the morning. In the majority of our controls the acrophase time also occurred in the early hours of the morning. In two controls (11B and 13B), one or both collections, in which the acrophase time was later than 9am, the cosinor values were also low suggesting the possibility of inaccurate collections. However, the 6-SM excretion, although low was better in the first 24 hours where the cosinor rhythm was no better. Full collection, but inaccurate labelling of the time could explain this but normal variation is a more reasonable explanation.

In the patients with sleep disorder, one patient had an acrophase time of 10.36am during the first collection with a cosinor value of 51.9. The following collection had a cosinor value of 93.2 and an acrophase time of 2.36am suggesting the possibility of inaccurate collection or timing of samples during the first 24-hour period, but confirming the normal excretion of melatonin in the second collection. Collecting two 24-hour samples from patients is a sensible precaution when attempting to show normal excretion of melatonin. Exogenous melatonin is usually administered shortly before the patient's normal bedtime. However we know that endogenous melatonin reaches its peak excretion in the early hours of the morning; we also know that exogenous melatonin has a very short half life and is

quickly excreted in the urine. It is therefore possible that the advantageous effect of exogenous melatonin occurs too early in the night to provide maximum benefit to the patient. Perhaps by repeating the dose, should the patient wake or by administering a slow release formula, the natural rhythm of endogenous melatonin secretion could be more closely mimicked, allowing further improvement of the sleep patterns in these patients.

Conclusion

Although our numbers of controls and patients are small the total daily volume of 6-sulphatoxymelatonin and acrophase time do not differ significantly between the two groups or from adult data. In addition, all but one (who had responded to melatonin) of the patients with sleep disorder showed a normal circadian rhythm of melatonin secretion, yet showed an improvement in total sleep time and sleep latency when treated with exogenous melatonin. These results suggest that the exogenous melatonin did not act by correcting abnormal endogenous melatonin secretion. We would propose that exogenous melatonin acts in these children by a simple sedative effect.

CHAPTER TEN

Summary of Thesis and Final Discussion

It is important to study TSC because potential treatment is available and there are a number of unanswered questions about the natural history of the condition. It is likely that resolving some of these issues could result in an improved quality of life and even life expectancy. I chose to study this condition as the subject for my thesis because I have a particular interest in epilepsy and neuro disability which are key issues for many patients with TSC.

Epidemiology of the TSC population in the Bath Health District

The reason why I undertook this ten year review was to look at the natural history of TSC in detail and to establish which clinical factors contributed most to the morbidity (and mortality) of this population so that I might examine some of these problems in greater detail. The advantage of undertaking a longitudinal study rather than a cross sectional study is that it allowed me to examine the impact of such factors observed over time. A database has now been set up at Bath to be updated regularly with information retrieved at clinic appointments and from research studies, which I hope will allow a more detailed picture of the disease to be compiled, giving greater understanding of the less common complications such as LAM. I also hope that it will allow the impact of clinical intervention in these patients to be more fully assessed.

In addition, this review gave us an opportunity to assess how the introduction of the diagnostic criteria might change the overall prevalence of the disease[4]. There will be a number of patients who previously had a diagnosis of TSC who are no longer considered to do so. In our small population of just nineteen patients ascertained in 1986, three patients had their diagnosis withdrawn; these are small numbers but if representative of the whole population of TSC patients, this might mean that as many as 15% had an incorrect diagnosis. This would significantly reduce the prevalence of the disease. It is therefore important that with the introduction of new diagnostic criteria, large and detailed epidemiology studies are repeated in order to provide a clear picture of the prevalence and incidence of the disease.

Epilepsy , its association with learning difficulties and its treatment

The seizure disorders of TSC are closely associated with the learning difficulties experienced by many of these patients. Infantile spasms are associated with the greatest degree of mental handicap in patients with TSC but the optimum medical treatment for infantile spasms remains uncertain. Steroids have been used for many years and my search of the literature found them to be effective in stopping the spasms in just half of all patients. One reason for the poor response to oral steroids might be that fears of serious side effects have resulted in inadequate doses being administered, so I undertook a retrospective review of the use of larger doses of oral prednisolone in patients with infantile spasms in Bath. This review found it to be effective in stopping the spasms in 70% of patients with no serious adverse effects being reported; although small it provided reassurance that larger doses of oral steroids could be used safely in the treatment of infantile spasms and suggested that larger doses might be more effective in stopping the spasms. I would suggest that larger study would be required to assess its efficacy more fully. Assuming approximately 50% of patients would achieve cessation of seizures if treated with 2mg/kg of prednisolone, such a trial would need to recruit at least 250 children, with approximately half randomised to "low dose (2mg/kg)" prednisolone and the other half to "high dose (60mg/day)" to attain 90% power to detect an improvement in cessation of seizures of 70% in the "high dose" group. Such a trial would require collaboration between many centres over a long period of time.

Vigabatrin, a relatively new anticonvulsant has also been used in the treatment of infantile spasms over the past 20 years, with similar results to steroids. However, recent studies had suggested that it might be particularly efficacious in the treatment of infantile spasms in tuberous sclerosis. I reviewed the English literature and found support for this theory, although the majority of the studies undertaken were non-randomised and had little power. Nonetheless, it suggested that vigabatrin should be the drug of choice for stopping the spasms in infants either with a known diagnosis of TSC or at high risk of TSC. Unfortunately although IS are associated with a high degree of mental handicap in patients with TSC none of these trials assessed the effect of vigabatrin on either long term psychomotor development or the onset of subsequent seizure types.

United Kingdom Infantile Spasms Study – A Stepping Stone to the Future

UKISS was a multicenter randomised trial set up to try and determine whether (if either) steroids or vigabatrin was most effective at stopping infantile spasms and whether either treatment was more efficacious with regard to the long-term outcome. I was responsible, under JPO's supervision for developing the trial design, protocol and trial packs which were put to the trial steering committee for comment and approval. I also remain closely involved with the trial as a member of the trial steering committee.

Unfortunately, patients with known TSC or at a high risk of TSC have been excluded from this study since it was felt that it would be unethical to withhold vigabatrin as treatment from this group of patients. The problem is that previous studies have not looked at long-term psychomotor development as an outcome. I therefore feel that it is important that further studies are performed specifically looking at the treatment of infantile spasms in this subgroup of patients, with particular respect to psychomotor development. If the UKISS trial does find vigabatrin to be more effective in stopping the spasms and giving improved development than steroids, it may be prudent to continue using vigabatrin as the "gold standard" against which newer treatments can be considered. If however, the UKISS trial finds no significant difference between the two groups or finds "steroids" to be more efficacious then there is a greater dilemma. Should a randomised controlled trial be then set up comparing steroids vs. vigabatrin in TSC – I feel that this would now be deemed ethical (in light of the visual field defects associated with the use of vigabatrin), but others might argue that a better trial would be one comparing treatment with vigabatrin alone say against a combination of vigabatrin and ACTH? Side effects must be taken into consideration. Although steroids are associated with a risk of mortality, especially if they are used for long periods of time, their side effects are well known and can be closely monitored. Unfortunately, although vigabatrin initially promised to be a relatively safe drug there are increasing concerns about the potential visual field defects associated with its use. At present it is unclear how frequently children will be affected, whether this complication is related to dosage or length of administration or whether it is reversible on withdrawing the drug.

Even if the UKISS trial does show one treatment to be beneficial overall as compared with the others, I believe that there are still many other issues that need to be addressed. There is often a delay in the presentation and/or diagnosis of the spasms so contributing to the delay

of initiating treatment. In the group of infants with TSC we hope that with improving diagnostic techniques (especially the possibility of genetic testing) diagnosis will be made at a younger age in many of these infants. It is important that both the parents (or carers) and the professionals looking after these infants are taught to recognise the onset of infantile spasms so that if they do occur treatment can be quickly initiated, preferably the same day as onset. It is possible that one of the reasons that infantile spasms have such a devastating affect on development is that their peak age of onset (4 -7 months) is also at a time when the brain is maturing rapidly. Obviously, it is not possible to change the natural history of the condition, but if the onset of infantile spasms could be delayed, or even prevented then it is possible that these patients will have an improved outcome. I would suggest that one way to prevent the spasms from occurring might be to treat young infants (within a few weeks of birth) known to have TSC and therefore be at high risk of developing the spasms from the time of diagnosis to say two years of age with a prophylactic therapy. However, such a therapy would have to be known to be safe and effective in treating the spasms (and even that would not guarantee that it would be effective at preventing the spasms (or the onset of learning difficulties) and must be safe to administer for long periods of time. At present there is no such treatment available.

A different approach to treatment of infantile spasms in infants with TSC might be epilepsy surgery. Some clinicians have suggested that it is the tubers that are responsible for the seizures and the learning difficulties suffered by these patients; others suggest that it is the seizures that are responsible for the delay or regression in psychomotor development. It is likely that the issue is more complex than this with many factors playing a role. In the 10 year review of the TSC patients in the Bath area, no patient without seizures had moderate or severe learning difficulties, yet we know that many of our patients without seizures have multiple tubers. It may be that in TSC tubers are responsible for acting as foci for seizures and also cause subtle intellectual impairment, but that it is the effect of the seizures on the developing brain that is associated with the greater loss of cognitive function. Further research is required to define the exact relationship of the tubers with both seizures and learning difficulties. Ongoing research into the treatment of epilepsy by surgery may help in solving this conundrum, at least in part. Epilepsy surgery has been a tool for treating some of those patients who have intractable epilepsy, resistant to anticonvulsant medication. In the past it has usually been reserved as "a last resort" – to be tried in those in whom all other treatments have "failed", although it is often very

successful in selected patients in stopping seizures. It has been less noteworthy in its impact on cognitive function, although there are anecdotal reports of patients improving mentally following such surgery. One reason why cognitive function may not improve after such surgery is that many patients are older and so the "damage" has already taken place in the developing brain. If patients with severe seizures are treated at an earlier age by surgery, it may be that their long term outcome may be improved. In the past, patients with tuberous sclerosis have not been considered "good" candidates for epilepsy surgery because they have multiple tubers each of which might act as a foci for seizures. As investigative techniques improve, for example EEG techniques, SPECT and functional scanning, may help in some patients. It might therefore be possible to set up a trial looking at the role of epilepsy surgery in the treatment of infantile spasms including patients with known TSC. Patients could be randomised to receiving either conventional treatment (i.e. steroids or vigabatrin) alone or both conventional treatment and surgery. Long term psychomotor development could then be measured. If patients treated with surgery had a higher rate of cessation of spasms and improved long term outcome, this would lend support to the theory that it is the affect of the seizure activity on the developing brain that has the greatest impact on intellect.

A Cochrane Review: an alternative approach to the evaluation of the medical treatments of infantile spasms.

The difficulty in setting up trials looking at the treatment of many of the complications seen in TSC is their relative rarity. Often the number of patients seen at any one centre is insufficient to give high enough power to an individual study, whilst collaboration relies on co-operation and often more importantly agreement between different centres. The main reason why lead clinicians declined to participate in recruiting patients into the UKISS trial was because they felt one treatment to be superior or safer to the other in treating the spasms and yet robust enquiry shows that there is no scientific data to substantiate these claims. One alternative way of overcoming such problems is to combine smaller studies by meta-analysis in order to increase the power of such studies. This was the reason that I chose to undertaking a Cochrane review on the medical treatment of infantile spasms. However, it is important to remember that the results that can be obtained from such a meta analysis are only as good as the studies included within the review. Unfortunately, the majority of studies that have previously been undertaken are not only small in number, looking at a large number of different therapies, but also of poor methodological quality,

and more importantly did not use standardised definitions, dosage regimes or outcome measures. Disappointingly, our review has not yet answered the question as to which treatment is optimum for infantile spasms. However, the review is ongoing and will continue to be updated on a six to twelve monthly basis, including newer (and hopefully larger, better quality) studies as they are undertaken. This still does not solve the problem of the different definitions or outcome measures used. Now might be the time to try and agree an international consensus as to how terms should be defined and how outcome should be measured, so that future studies can easily be compared.

A different approach to investigating the optimum treatment for infantile spasms is to consider them as a symptom of many underlying aetiologies rather than as a single entity. Past trials have produced inconsistent and varying results. One possible reason for this is that trials have looked at patients with a wide range of underlying causes for their infantile spasms. Only one trial[40] to date has considered the treatment of infantile spasms due to a single underlying cause (tuberous sclerosis), which suggested that vigabatrin was more effective in stopping the spasms in this sub-group of patients. Again the problem in trying to study single underlying pathophysiological causes of the spasms is the rarity of the problem. In order to be able to study the treatment of infantile spasms in this way, large collaborative trials will need to be set up. Other possible sources of heterogeneity also need to be considered in future trials. At present it is unclear as to whether factors such as sex or age of onset of spasms contribute to the outcome as there is little data on the long-term outcome of untreated spasms. It may be, for example, that girls have a better outcome than boys regardless of treatment. In our small review of patients with TSC who suffered from epilepsy in the Bath region (many of whom had infantile spasms) there was a suggestion that the trend was for girls to have a better long-term outcome, both in terms of seizure control and psychomotor development.

Can Oral treatment of Non-convulsive status epilepticus improve long term outcome?

Other seizure types (generalised tonic clonic seizures, complex partial seizures etc.) are common in TSC but the precise relationship of these to the learning disabilities seen in TSC remains unclear. The knowledge that some infants can develop normally to over a year and even sometimes to two or three years of age before seizures commence when they then dramatically lose skills does not deter some from believing that it is the continuing seizure activity, which is usually present, which interferes with both the learning and the

expression of and the testing of ability; but that if the seizure activity ceased, the child would resume learning. They believe that seizures do not cause permanent harm but that our inability to control the seizures prevents us from seeing that. It has also been proposed that the underlying brain lesions prevent further development at the same moment that the seizures begin – a coincidence not likely to be explained by the site, or size, or number of lesions. The loss of skills is explained by the theoretical possibility that cortical development fails to take over from sub-cortical activity (akin, to the apparent loss of vision in those with cortical blindness when sub-cortical fixation ceases). However, parents and clinicians who have seen a perfectly normal child lose the majority of their skills often believe that it is the seizures themselves that cause harm in some way and that controlling the seizures (our only hope) might improve intellectual outcome. This is reflected in those who suffer episodes of non-convulsive status. With the onset of continuous seizure activity there is often a dramatic loss of skills, which are rapidly regained if the seizure activity is successfully terminated. However, if the episodes recur regularly or are not treated quickly then the patients do not always regain the skills they previously had. Also some adults do stop seizing but do not "wake up" and recover their skills. Obtaining evidence of the beneficial effect (if any) of seizure control or prevention is therefore an important issue for which evidence is currently lacking, partly because of the lack of effective interventions but also because of the difficulties of setting up clinical trials that are ethically sound in these patients. Nevertheless it is an issue that urgently needs addressing. I therefore looked at a small number of patients in order to assess the effectiveness of oral diazepam in the treatment of NCSE, this observational study suggested that it was effective in terminating such episodes. However, it did not address the issue of whether earlier abortion of the episodes prevented or ameliorated subsequent intellectual regression. I would put forward that a larger study needs to be undertaken with patients randomised to either receiving oral treatment for each of their episodes of NCSE or more conventional intravenous benzodiazepines. Again, because of the rarity of NCSE, such a trial would need to be collaborative. Patients could be enrolled during their first episode of NCSE. On admission to hospital an EEG could be performed to confirm the diagnosis of NCSE, the patient would be randomised to receive either oral or intravenous treatment, following which a second EEG could be performed to ensure that the NCSE has been successfully terminated. Those patients randomised to receive oral treatment would then have subsequent episodes treated by the carers at home, whilst those receiving intravenous treatment would be readmitted to hospital. Cognitive function could then be performed at regular intervals, say

six monthly by a blinded assessor to try and establish whether or not there was a more rapid or severe decline in function in either group. This would then need to be compared to the amount of time spent in NCSE to see if there was a link between the two phenomena.

Lymphangioleiomyomatosis, a question of gender?

LAM is a rare complication of TSC. Our cohort of 21 patients is (to our knowledge) the largest in the literature to date. We had hoped to highlight those patients at greatest risk of developing LAM. We found that it does seem to be limited to females, mainly of child bearing age. We only found one male with a definite diagnosis of LAM (both in our series of patients and in the literature) and he was unusual because he also had a diagnosis of Kleinfelters syndrome. However we found no other definite risk factors. We had hoped to propose a model for screening those patients at high risk but further research is required to ascertain if change on HRCT or abnormal lung function is present in the presymptomatic stage of the disease. Our cohort of patients did provide useful information regarding the natural history of LAM in TSC. In the literature LAM has been described as a relentless disease with death occurring within years of the onset of symptoms. We found its course to be extremely variable in our patients with TSC. We also found some anecdotal evidence that it might occur as localised disease in patients with TSC rather than always being generalised, and that these patients responded well to conventional treatments such as lobectomy. We had hoped to study the effects of hormonal treatment on the course of LAM, but unfortunately our numbers were too small to provide any useful information. A search of the literature suggests that hormonal manipulation may well be beneficial in a significant proportion of patients, however this is based mainly on case reports. The effects of hormonal treatment on LAM needs to be investigated further. We would suggest that the natural history of LAM may be different in patients with TSC than those without and that a trial would need to be set up looking specifically at this group of patients. Because of its rarity such a trial would need to be multicentre or even international in order to recruit the numbers required. It would need to be a randomised blinded trial with one arm of the trial receiving placebo treatment since the natural history of the condition remains uncertain. One way forward would be to set up a central register, such as has been set up for patients with renal complications, this would at least allow accumulation of information about the natural history of the condition.

Screening for End Stage Renal Fialure – a Conundrum

Renal disease contributes a significant proportion of morbidity seen within the TSC population. Fortunately we found ESRF to be rare in TSC, only affecting approximately 1% of the population. Although PKD (known to cause ESRF) was over-represented in the population of TSC with ESRF as compared with the whole of the TSC population it accounted for less than half of cases, making screening for the prevention of ESRF problematic. Screening for PKD is no doubt useful, and all infants or young children diagnosed with TSC should have renal USS performed to exclude the presence of PKD. Screening for other causes requires further thought and until such time routine USS should not be done, but patients with symptoms such as pain or bleeding should be thoroughly investigated.

Sleep Disorders in TSC and the Use of Melatonin

There are many behavioural problems associated with tuberous sclerosis; they most commonly arise in patients who also have epilepsy and learning difficulties. Many of these patients have autistic tendencies, hyperactivity and self-harm. Many have associated sleep disorders, which carers find the hardest to cope with. Melatonin had been shown to be beneficial in treating the sleep disorders in other patients in small studies. Our group looked at the effect of melatonin on the sleep disorders in TSC. In two small studies we found it to be most helpful in increasing the total sleep time and sleep latency and is less helpful in preventing the frequent night awakenings suffered by many of these patients. We found 5mg to be a beneficial dose but that 10mg did not improve sleep patterns further. It also looks as though melatonin has few side effects, does not interfere with the pharmacokinetics of concurrent anticonvulsants and does not affect seizure frequency. However, larger randomised controlled trials are required to confirm these findings and also to assess long-term efficacy. A study undertaken over a longer time period might also be helpful in determining why melatonin was more effective in some individuals than others. We know that melatonin excretion in "normal individuals" is relatively stable from day to day. We also know that as a group TSC patients with sleep disorder have melatonin excretion patterns that fit within the normal distribution but we do not know how stable melatonin secretion is day to day in this group of patients. It has been suggested that many blind patients also have circadian rhythms, but that they have a different "time frame" i.e. each co-sinor wave is longer/shorter than 24 hours with the result that on some days their peak melatonin excretion will occur at the "normal" time i.e. the early hours of the

morning, but at other times it will occur at different periods of the day, e.g. mid-afternoon. It has been suggested that in these patients timing of commencement of melatonin therapy with respect to the individuals circadian rhythm is crucial in determining whether or not melatonin therapy is likely to be successful or not.

We also attempted to examine the mechanism by which melatonin has its effect. It had been suggested that exogenous melatonin worked by resetting the sleep-wake cycles. However we found normal circadian rhythms in our small cohort of patients suggesting that it works by a simple sedative effect. Again theses findings need to be confirmed by larger studies. Interestingly endogenous melatonin reaches its peak excretion in the early hours of the morning whilst exogenous melatonin is given late at night reaching its peak levels earlier in the night. A slow release preparation of melatonin is now available which might in theory prove to be more effective particularly with regard to total sleep time and number of awakenings. Further studies need to be undertaken comparing slow release preparations both against placebo and traditional preparations to establish whether they improve sleep patterns further.

Conclusion

Even though great advances have been made in our understanding of tuberous sclerosis since Von Recklinghausen first described it over a century ago, it is still associated with high morbidity and mortality. It is unlikely, even with the advances in genetics that the incidence of severely affected patients is likely to fall much in the near future. It is clear that collaborative efforts, using the best protocols, need to be made if clinicians are to make significant advances in reducing both the morbidity and mortality associated with this disorder.

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Glossary

Adrenocorticotrophin Hormone (ACTH): a synthetic steroid given as an intramuscular injection for the treatment of infantile spasms.

Allele: alternative form of a gene occupying the same locus on a particular chromosome.

Amblyopia: loss of the development of vision in one eye.

Amniocentesis: a needle is inserted through the abdominal wall into the amniotic sac to withdraw some of the amniotic fluid for diagnostic purposes: it may be carried out after fourteen weeks gestation.

Angiofibroma (AF): a characteristic facial rash pathonognomic for tuberous sclerosis see figure one.

Angiomyolipoma (AML): highly vascular benign tumours consisting of smooth muscle and adipose cells found in the kidneys, see figure twelve.

Autosomal dominant: a dominant gene is transmitted by an affected individual to half of his/her offspring.

Bath Health District Authority: covers a population of ~417,000 people and has ~ 5,500 live births per annum.

Chorionic Villus Sampling: involves taking chorionic tissue (part of the placenta) for diagnostic purposes; it may be carried out from eight weeks gestation.

Chromosome: a structure containing DNA and protein, situated in the nucleus of the cell, carrying genetic information.

Chylothorax: accumulation of chyle (fat laden fluid) within the lungs.

Cochrane Collaboration: A group that focuses on systematic reviews of randomised controlled trials because they are likely to provide more reliable information than other sources of evidence on the differential effects of alternative forms of health care.

Cochrane Controlled Trials Registrar (CCTR): a database of references to controlled trial in health care.

Cochrane Database of Systematic Reviews (CDSR): a database containing all the currently available Cochrane reviews.

Cochrane Review Library (CRL): is a collection of databases containing the Cochrane Database of Systematic reviews, the Cochrane Controlled Trial Register, the Database of Abstracts of Effectiveness, the Cochrane Review Methodology Database and information about the Cochrane Collaboration.

Complex partial seizures (CP): (previously called temporal lobe epilepsy) vary considerably in their clinical features. There is often an aura preceding the attack, during which the patient may be fully conscious. The patient will often exhibit extreme

of emotion during an attack for example anger or fear. They often exhibit purposeful movements such as seeking close contact or pacing. Autonomic phenomena are also frequent. Some patients can recall the whole episode, others suffer amnesia.
Computerised Tomography (CT): imaging of deep structures of the body by recording the echoes of pulses of electrons reflected by tissue planes where there is a change in density.

Cor pulmonale: right sided heart failure secondary to pulmonary hypertension.

Cyanosis: a bluish discolouration of the skin and mucus membranes due to decreased oxygenation of haemoglobin.

Deoxyribonucleic acid (DNA): Genetic information is stored in the form of double stranded DNA. Each strand of DNA is made up of a deoxyribose phosphate backbone and a series of purine (adenine and guanine) and pyrimidine (thymine and cytosine) bases that are held together by hydrogen bonds.

Disseminated Intravascular Co-agulation: activation of co-agualtion factors leading to platelet consumption and secondary fibrinolysis. It results in widespread spontaneous bleeding into the skin, from the mouth and nose and into the brain and other organs.

Drop attacks: These are typically violent and sudden in onset consisting of a sudden brief violent contraction of the muscles of the neck and trunk, often with a jerk of the arms. They cause the patient to fall and hurt himself as they make no attempt to save themselves by putting out their arms.

Dyspnoea: shortness of breath

Echocardiogram: recording of the position and motion of the heart walls, internal structures of the heart and neighbouring tissue by the echo obtained from beams of ultrasonic waves directed through the chest wall.

Electrocardiogram (ECG): a graphic record of the variations in electrical potential caused by the electrical activity of the heart muscle as detected at the body surface. See figure fourteen.

Electroencephalogram (EEG): a graphic record of changes in the electric potential in various areas of the brain by means of electrodes placed on the scalp. See figure seventeen.

Embase: an electronic database citing published scientific studies from 1981.

Fibrous Forehead Plaque (FFP): raised reddish area of skin occurring on the forehead or scalp. See figure six.

Gene: part of a DNA molecule which directs the synthesis of a specific polypeptide chain.

Generalised tonic-clonic seizures (GTC): (previously called grand mal seizures) These may be primary and generalised from the outset or occur secondarily from generalisation of a partial seizure. They consist of a tonic phase with generalised rigidity with sudden loss of consciousness, the patient falling if standing. This short phase is

followed by the clonic phase with rapid generalised jerking movements. After a variable time the clonic phase ends and the patient becomes post-ictal often sleeping for a period of time. There may be apnoea with cyanosis and incontinence of urine and faeces.

Genotype: the genetic constitution of an individual.

Giant Cell Astrocytoma (GCA): a brain tumour composed of astrocytes of varying differentiation. They usually follow a relatively benign course in tuberous sclerosis, but surgical removal is necessary.

Haemoptysis: blood stained sputum.

Hamartoma: a benign tumour composed of an overgrowth of tissue cells normally present in the affected part, but often with one element predominating.

Hemiplegia: weakness of one side of the body.

Heterozygosity: the possession of two different alleles at the corresponding loci on a pair of chromosomes.

Homozygosity: the possession of two identical alleles at the corresponding loci on a pair of chromosomes.

Hypertonia: increased tone.

Hypomelanic Patch or White Patch: Patches of skin that appear pale in colour as a result of a decrease in melanosomes in the skin. The are best visualised with ultraviolet light and are not unique to patients with tuberous sclerosis. See figure three.

Hypotonia: decreased tone.

Hypsarrhythmia: very high voltage, random, slow waves and spikes seen in all cortical areas giving a totally chaotic appearance on the EEG, see figure seventeen.

Incidence: the number of new cases of a specific disease occurring during a given period of time.

Infantile spasms (IS): Spasms may be flexor, extensor, lightning or nods, but most commonly are mixed. Each individual spasm last seconds only but they commonly occur in batches of up to 100s in one run. There is often an associated cry and they commonly occur on waking or falling asleep.

Language bias: studies in which an intervention is not found to be effective are less likely to published in English.

Lennox Gastaut syndrome: manifests itself in children aged 1 to 8 years. The most common seizure types are tonic-axial, atonic and absence seizures, but other types such as myoclonic, generalised tonic clonic or partial are frequently associated with this syndrome. Seizure frequency is high and status epilepticus frequent. In general there are severe learning difficulties and the seizures are difficult to control.

Locus: the site of a gene on a chromosome.

Lymphangioleiomyomatosis (LAM): a rare cystic disease of the lung that is usually generalised and progressive, can be extremely difficult to treat and is generally considered to have a poor prognosis. It is almost exclusively reported to occur in women of childbearing age. See figure fifteen.

Magnetic resonance imaging (MRI): imaging of deep structures of the body by recording electrons reflected by electrons as they pass through different tissue planes.

Medline: an electronic database citing published medical studies.

Mutation: a permanent transmissible change in the genetic material.

Non-convulsive status epilepticus (NCSE): characterised by a patient who has continuous or almost continuous epileptic activity both clinically and on the EEG but clinical signs of an overt seizure disorder may be extremely subtle. The onset may either be so subtle as to suggest dementia or may be abrupt. Lack of awareness may extend to loss of appetite with weight loss. Patients may cycle from periods of complete unresponsiveness to one of partial responsiveness. Frequent brief, but small, myoclonic jerks can often be felt but not seen. Often there are associated autonomic features such as excessive salivation and sweaty palms.

Penetrance: the proportion of individuals with a particular genotype who also have the corresponding phenotype.

Phenotype: the appearance of an individual resulting from the effects of both environment and genes.

Pleural effusion: accumulation of fluid within the lungs.

Pleurectomy: excision of a portion of the pleura.

Pleurodesis: fusion of the two layers of the pleura together (usually chemically).

Pneumothorax: air or gas in the pleural space, i.e. within the membrane that surrounds the lung.

Polycystic Kidney Disease (PKD): Inherited in an autosomal dominant manner, it manifests in infancy as tiny cystic lesions distributed throughout both kidneys. With advancing age the cysts enlarge at a variable rate resulting in loss of renal function.

Prevalence: the total number of cases of a specific disease in existence in a given population at a given point in time.

Randomised controlled trial (RCT): Trials in which participants are prospectively allocated to treatment groups by random (e.g. random number generation, coin flips) or quasi random (e.g. by date of birth) process.

Selection bias: systematic differences between comparison groups in prognosis or responsiveness to treatment.

Selective arterial embolisation: therapeutic introduction of a substance into a vessel in order to occlude it.

Simple partial seizures or absence attacks: These generally consist of a sudden, brief, blank stare accompanied by unawareness and sometimes flickering of the eyelids or other automatism, lasting seconds or occasionally minutes only.

Suppressor gene: a gene that plays an important role in the regulation of the normal cell cycle. For a suppressor gene to exert its influence on a cell, both alleles must be affected i.e. loss of heterozygosity.

Ultrasound scan (USS): imaging of deep structures of the body by recording the echoes of pulses of ultrasound reflected by tissue planes where there is a change in density.

West syndrome: (also called infantile spasms) consists of a characteristic triad; infantile spasms, arrest of psychomotor development and hypsarrhythmia on the EEG, though one element may be missing.

Wolff Parkinson White Syndrome (WPW): This is caused be an abnormal myocardial connection between the atria and ventricles of the heart causing abnormal depolarisation of the ventricles. About half of those with WPW will suffer from tachycardias (abnormally fast heart rates), see figure fourteen.

Woods light: an ultraviolet light that is shone on the skin. Hypomelanic patches shine bright white under light.

Abbreviations

1.	ACTH	Adrenocorticotrophin Hormone
2.	AF	Angiofibroma
3.	AML	Angiomyolipoma
4.	Bd	Twice Daily
5.	CMZ	Carbamezepine
6.	CPS	Complex Partial Seizures
7.	CRF	Chronic Renal Failure
8.	CT	Computerised Tomography
9.	CXR	Chest Xray
10.	DIC	Disseminated Intravascular Co-agulation
11.	DNA	Deoxyribonucleic Acid
12.	ECG	Electrocardiogram
13.	Echo	Echocardiogram
14.	EEG	Electroencephalogram
15.	ESRF	End Stage Renal Failure
16.	FFP	Fibrous Forehead Plaque
17.	GCA	Giant Cell Astrocytoma
18.	GP	General Practitioner
19.	GTC	Generalised Tonic Clonic Seizures
20.	HMP	Hypomelanic Patch or White Patch
21.	HRCT	High Resolution Computerised Tomography
22.	IM	Intra-muscularly
23.	IS	Infantile Spasms
24.	Iv	Intra-vascular
25.	IVP	Intra-venous Pyelogram
26.	JPO	Professor John P Osborne
27.	LAM	Lymphangiomyomatosis
28.	MMR	Measles, Mumps and Rubella Vaccination
29.	MR	Mental Retardation
30.	MRI	Magnetic Resonance Imaging
31.	N/A	Not Available / Applicable
32.	NCSE	Non-Convulsive Status Epilepticus
33.	Od	Once Daily
34.	PKD	Polycystic Kidney Disease
35.	Qds	Four Times Daily
36.	RCT	Randomised Controlled Trial
37.	REM	Rapid Eye Movement (sleep)
38.	RUH	Royal United Hospital
39.	SLD	Severe Learning Difficulties
40.	SVT	Supraventricular Tachycardia
41.	Tds	Three Times Daily
42.	TLE	Temporal Lobe Epilepsy
43.	TRH	Thyroid Releasing Hormone
44.	TSC	Tuberous Sclerosis Complex
45.	UK	United Kingdom
46.	USS	Ultrasound scan
47.	UTI	Urinary Tract Infection
48.	VGB	Vigabatrin
49.	WPW	Wolff Parkinson White Syndrome

Tables for thesis

Chapter two – A ten year review of the epidemiology, morbidity and mortality of the tuberous sclerosis population in the Bath Health District.

Chapter three – Epilepsy and learning difficulties.

Chapter Five – Cochrane review

Chapter Six – Non-convulsive status epilepticus

Chapter Seven – Lymphangioleiomyomatosis and tuberous sclerosis.

Chapter Eight – Renal disease.

Chapter Nine – Sleep disorder in tuberous sclerosis complex.

Figures for thesis

APPENDIX TWO

Professor John Osborne: a Consultant Paediatrician and Honorary Senior Lecturer at the University of Bath. He has conducted research into Tuberous Sclerosis (a significant cause of infantile spasms) since 1985, leading the team which located the TSC 1 gene. He was responsible for the follow-up and development assessment of 276 infants in the UK study of ethamsylate for the prevention of intraventricular haemorrhage, which achieved a 97% follow-up rate.

Dr Richard Appleton: a Consultant Paediatric Neurologist in Liverpool with a special interest in epilepsy. He has conducted studies of vigabatrin in infantile spasms.

Dr Eleanor Hancock.

Dr Tony Johnson: is a statistician for the Medical Research Council in Cambridge and he has extensive experience of trials of epilepsy, although predominantly in older children and adults.

Dr Colin Kennedy: is Consultant Paediatric Neurologist in Southampton and was responsible for the multicentre study of post-haemorrhagic hydrocephalus in premature infants.

Dr Richard Newton: is a Consultant Paediatric Neurologist in Manchester and a member of the Cochrane Collaborative Group for Epilepsy. He has published a meta-analysis of the treatment of febrile convulsions.

Dr F O'Callaghan: is Research Registrar in Tuberous Sclerosis to Prof. Osborne, and has recently won a Wellcome Research Epidemiology Training Fellowship to study Tuberous Sclerosis, based in Prof. Osborne's department, with Dr C Martyn of Southampton University as joint supervisor.

Dr Christopher Verity: is a Consultant Paediatric Neurologist in Cambridge and has published on the epidemiology of epilepsy. He is currently Chairman of the British Paediatric Association's Surveillance Unit.

Dr Lisa Vickers: is working for Prof. Osborne as a research co-ordinator on a one year pump-priming grant to establish this study of infantile spasms. She is a pharmacologist with expertise in research management.

APPENDIX THREE

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APPENDIX FIVE

SLEEP DISTURBANCE IN TUBEROUS SCLEROSIS QUESTIONNAIRE

Name

Childs name

Childs d.o.b.

Address

Tel. No.

Please circle the appropriate number for questions 1-4

0 = no problem
1 = occurs less than twice a week
2 = occurs three or more times a week

1. Does your child take more than an hour to settle and finally fall asleep?
   Answer = 0 1 2

2. Does your child wake for more than a few minutes at night?
   Answer = 0 1 2

3. Do you have to get up to attend to your child at night?
   Answer = 0 1 2

4. Do you take your child into your bed at night?
   Answer = 0 1 2

5. At what time is your child put to bed?
6. Is your child in nappies? yes / no
7. We would like to participate in this study yes/no
8. We would be able to obtain a 48 hour urine collection yes/no
9. We would be able to obtain a urine sample approx. every 4 hours yes/no

Signature **Date**

SLEEP DIARY

WEEKS 1 & 2
(No treatment)

= time put to bed

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D.o.b.
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SLEEP DIARY

WEEKS 3 & 4
(Treatment A + B)

Give melatonin capsules half an hour
Before time put to bed

= time put to bed

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SLEEP DIARY

WEEKS 5 & 6
(No treatment)

= time put to bed

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SLEEP DIARY

WEEKS 7 & 8
(Treatment C + D)

Give melatonin capsules half an hour before time put to bed

= time put to bed

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FIT DIARY

WEEKS 1 & 2
(No treatment)

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FIT DIARY

WEEKS 3 & 4
(Treatment A + B)

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FIT DIARY

WEEKS 5 & 6
(No treatment)

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FIT DIARY

WEEKS 7 & 8
(Treatment C + D)

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Publications

Peer Reviewed Articles:

Melatonin and sleep disorder in tuberous sclerosis.
Dr FJK O'Callaghan, Dr A C Clarke, Dr E Hancock, A Hunt, Dr JP Osborne.
Published: Developmental Medicine and Child Neurology 1999; 41: 123-126.

Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review.
Dr Eleanor Hancock and Dr John Osborne.
Published: Journal of Child Neurology 1999;14(2):71-4.

End Stage Renal failure in Adults with Tuberous Sclerosis Complex.
Dr Antonia Clark, Dr Eleanor Hancock, Dr Christopher Kingswood and Dr John Osborne.
Published: Nephrology, Dialysis and Transplantation 1999; 14: 988-991.

Cognitive deficits in normally intelligent patients with Tuberous Sclerosis.
Dr John Harrison, Dr Eleanor Hancock, Dr Finbar O'Callaghan, Dr John Osborne and Dr Patrick Bolton.
Published: American Journal of medical Genetics 1999;88(6):642-6.

The treatment of West syndrome: a Cochrane review of the literature to December 2000.
Dr Eleanor Hancock, Prof John Osborne and Prof. Phillip Milner.
Published: Brain and Development 2001;23:624-634.

Lymphangiomyomatosis in tuberous sclerosis.
Dr Eleanor Hancock, Dr Sue Tompkins , Prof. Julian Samson and Prof. John Osborne.
Published: Respiratory Medicine 2002;96:7-13.

Lymphangiomyomatosis: a literature review.
Dr Eleanor Hancock and Prof John Osborne.
Published: Respiratory Medicine 2002;96:1-6.

Cochrane Review: The treatment of infantile spasms.
Dr Eleanor Hancock, Prof John Osborne and Prof. Phillip Milner.
Published: Issue 2;2002: The Cochrane Library.

The effect of melatonin dosage in the Sleep disorder in tuberous sclerosis complex.
Dr Eleanor Hancock, Dr Finbar O'Callaghan, Dr J English and Prof. Osborne.
To be submitted.

Melatonin excretion in children.
Dr Eleanor Hancock, Dr Finbar O'Callaghan, Dr J English and Prof. Osborne .
To be submitted.

Invited Articles:

Infantile Spasms: recognition, diagnosis and treatment.
Dr Eleanor Hancock and Dr Osborne.
Published: Current Paediatrics 1998;8:48-54.

The treatment of infantile spasms.
Dr Eleanor Hancock.
Submitted: Clinical Evidence, BMJ.

Letters:

Treatment of infantile spasms with high dose oral prednisolone.
Dr Eleanor Hancock and Dr John Osborne.
Published: Developmental Medicine and Child Neurology 1998;40:500.

Infantile spasms and vigabatrin: Study will compare effects of drugs.
John P Osborne, Stuart W Edwards, Eleanor Hancock, Andrew L Lux, Finbar O'Callaghan, Tony Johnson, Colin R Kennedy, Richard W Newton, Christopher Verity.
Published: British Medical Journal 1998;318;56-57.

Revised guideline for prescribing vigabatrin in children.
Dr A Lux, Dr S Edwards, Dr J Osborne, Dr E Hancock, Dr A Johnson, Dr C Kennedy, Dr F O'Callaghan, Dr R Newton and Dr C Verity.
Letter BMJ 2001;322:236.

Presentations:

Treatment of infantile spasms with high dose oral prednisolone: a retrospective view.
Poster presentation January 1997, BPNA Oxford.

The historic treatment of infantile spasms.
Presented at a conference on infantile spasms February 1997, West Midlands.

Presentation of the UKISS trial.
The Wessex Neurological Meeting June 1997, Bath.

The treatment of infantile spasms.
The Wessex Paediatric Club July 1997, Winchester.

A review of vigabatrin in the treatment of infantile spasms in tuberous sclerosis.
The Paediatric Research Society February 1998, Swansea .

The pulmonary complications of tuberous sclerosis.
World Congress on Tuberous Sclerosis October 1998, Gothenburg .

Melatonin excretion in normal children and in the sleep disorder of tuberous sclerosis.
Paediatric Research Society September 2000, Newcastle.

Cochrane review of the medical treatments of infantile spasms.
International Symposium on the West Syndrome, Tokyo, Japan February 2001.

The United Kingdom Infantile Spasm Study

TRIAL FOLDER CONTENTS

The United Kingdom Infantile Spasm Study

INTRODUCTION TO UKISS

Thank you for participating in UKISS. This is two studies in one and is aiming to answer several important questions.

The ***Epidemiology Study*** aims to give a reliable estimate of the incidence of infantile spasms in the UK and to define important characteristics of children with infantile spasms. We'll be looking at age at onset, predisposing conditions and underlying aetiology, and clinical features of the spasms. We would also like to get a description of response to treatment in infants who are not enrolled in the drug trial.

The most important component of the study is the ***Randomised Controlled Trial*** of synthetic ACTH (Synacthen Depot), prednisolone (Prednesol) and vigabatrin (Sabril) in infants aged between 2 and 12 months. This randomised controlled trial is important because it is large enough to provide reliable estimates of treatment and adverse effects and will be looking at two other important outcomes: EEG improvement and neurodevelopmental progress.

The ***Summary Sheet*** and ***Flow Diagram*** give overviews of the study structure. The ***Action Plan*** shows which forms to complete at each stage of the study. The ***Protocol*** gives a fuller description of the study, its aims, and its design. Please do not hesitate to contact us if you have any questions or concerns. We look forward to hearing from you.

The ***Patient*** and ***Doctor Information Sheets*** are designed as a resource for use before consent is obtained and for reference at any point during the trial.

Much of the information about the progress of the child will be obtained from a ***Patient's Diary***.

We have tried to keep the amount of work required of the clinician to a minimum, but we appreciate that it is still a good deal of extra work for you. We assure you that we are extremely grateful for the time and commitment that you are devoting to the study. Every enrolling hospital will be acknowledged in the paper if editorial policy allows this, and on a website otherwise.

The United Kingdom Infantile Spasm Study

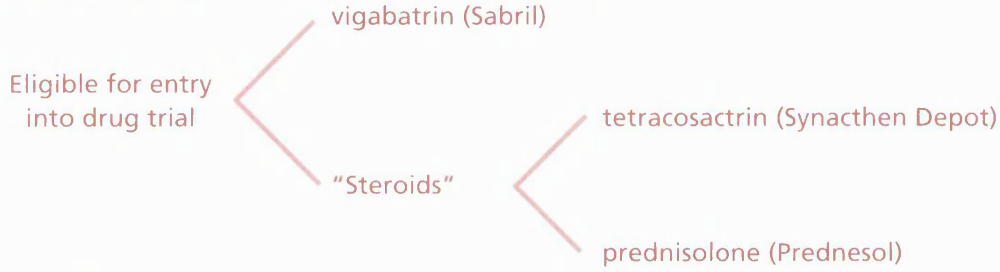
TRIAL SUMMARY

Epidemiology

INCLUDE ALL CASES (of any age) of newly diagnosed infantile spasms (IS)

Drug trial

Inclusion criteria: all new clinical diagnoses of IS with seizure onset between 2 completed calendar months and 1 year of age. Randomise within 72 hours. (EEG or video EEG is essential unless unable to arrange within 72 hours and your normal practice would be to start treatment without EEG.)



Drug doses:

vigabatrin 50 mg/kg/day orally in 2 divided doses for 2 doses then 100 mg/kg/day, but if no seizure control after 96 hours (ie after 6 further doses) then 150 mg/kg/day in 2 divided doses

prednisolone 10 mg orally 6 hourly (regardless of weight) for 2 weeks: increase to 20 mg 8 hourly if no seizure control at 7 days

Synacthen Depot 0.5 mg IM on *alternate days* for 2 weeks: if no seizure control at 7 days, increase to 0.75 mg on *alternate days*

Exclusion criteria:

(i) Known or suspected tuberous sclerosis at randomisation (see protocol for criteria)
(ii) Infants previously treated with vigabatrin or steroids within 28 days of diagnosis of IS
(iii) Contraindication to prednisolone, tetracosactrin or vigabatrin
(iv) Lethal or potentially lethal other condition
(v) Previous treatment for IS
(vi) Inability of parent/guardian to give informed consent
(vii) Expected to leave the UK within 1 month of randomisation
(viii) Inability of parent/guardian to know to nearest whole day time of cessation of seizures
(ix) Enrolment in concurrent trial likely to affect outcome of IS

Outcomes:

Primary outcome:

(i) number of patients achieving complete cessation of seizures for 48 hours within 14 days of starting treatment

Secondary outcomes:

(ii) developmental progress by 14 months of age
(iii) Reduction of number of spasms in two-week period
(iv) Relapse rates
(v) Other seizure types and frequency at 14 months of age
(vi) Resolution of hypsarrhythmia by 14 days

UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG

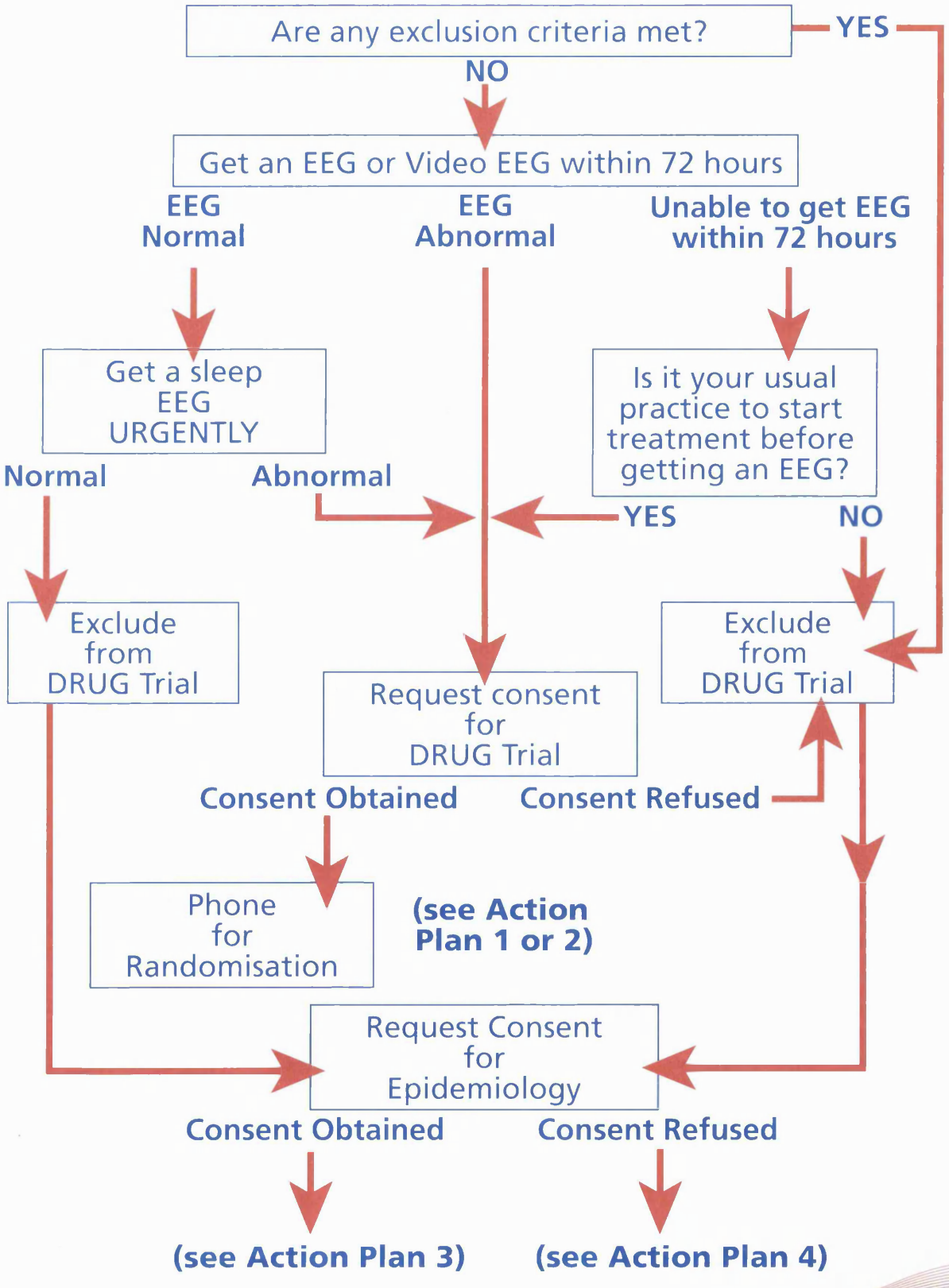
Enquiries: **Tel/Fax 01225 824206**
Randomisation: **Tel 01225 824490**

*See **Protocol** for confirmation and more details*

UKISS

The United Kingdom Infantile Spasm Study

A CLINICAL DIAGNOSIS OF INFANTILE SPASMS made by a consultant or his/her deputy



The United Kingdom Infantile Spasm Study

Action Plan

Patient Presentation	Consent and Enrolment	14-day Follow-up	28-day Follow-up	3-monthly Follow-up	12 to 14 month Follow-up
patient meets inclusion criteria for RCT (see Protocol section 1); no exclusion criteria for RCT (see Protocol section 2); parents consent to randomisation and inclusion in trial.	• complete **Consent Check List** • complete **Consent Form A** with parents • complete **Form 1**, then phone Trial Centre for randomisation • complete **Form 2** • arrange treatment to be given and counsel parents in use of **Patient's Diary** • return photocopies of the above forms to the Trial Centre • *if taking blood during treatment period,* please obtain sample for DNA analysis (see **Form 5**)	• after 14 days of treatment, complete **Form 4** • check pages D3 to D6 of **Patient's Diary** • return photocopies of **Forms 4 & 5** and pages D3 to D6 to Trial Centre	• *after 28 days of treatment,* check page D8 of **Patient's Diary** • return photocopy of page D8 to Trial Centre	• at each 3-monthly follow-up, check appropriate General Progress sheet from **Patient's Diary** • complete **Form(s) 6** • send photocopies of these to Trial Centre	• *when child is 12 to 14 months old,* complete **Form 7** • check remaining pages of **Patient's Diary** • send photocopies of **Form 7** and remaining **Patient's Diary** pages to Trial Centre
patient meets inclusion criteria for RCT; no exclusion criteria for RCT but EEG not obtained within 72 hours; parents would consent to randomisation and inclusion in trial.	• **Please discuss with Trial Centre immediately** **Forms as above**				
patient has a clear exclusion criterion; parents consent to inclusion in **Epidemiology Study** *or* **parents or clinician are not happy for child to be included in RCT** but are happy to consent to **Epidemiology Study** *or* **other**, such as unable to arrange EEG in time, or forgot to randomise	• complete **Consent Form B** with parents • complete **Form 1** • complete **Form 3** • return photocopies of forms to Trial Centre • counsel parents in use of **Patient's Diary** • *if taking blood during treatment period,* please obtain sample for DNA analysis (see **Form 5**)	• after 14 days of treatment, complete **Form 4** • check pages D3 to D6 of **Patient's Diary** • return photocopies of **Forms 4 & 5** and pages D3 to D6 to Trial Centre	• *after 28 days of treatment,* check page D8 of **Patient's Diary** • return photocopy of page D8 to Trial Centre		• *when child is 12 to 14 months old,* complete **Form 7** • check remaining pages of **Patient's Diary** • send photocopies of **Form 7** and remaining **Patient's Diary** pages to Trial Centre
parents do not consent to inclusion in RCT or Epidemiology Study	• complete **Form 1** and return photocopy to Trial Centre				

The United Kingdom Infantile Spasm Study

Doctors' information sheet

Infantile spasms (IS), also known as West syndrome were first described by Dr. West in 1841 who gave an account of them occurring in his own 4 month old son. They are a refractory seizure disorder with a high risk of a poor prognosis, including intractable epilepsy and severe developmental delay. The condition is relatively common with an incidence which may be as high as 1 in 2500 births. There is an association with a number of disorders. Some of the disorders, such as cerebral palsy or Down syndrome are known at the disease onset, whilst others, such as Tuberous Sclerosis or neuronal migration disorders are discovered on investigation after the onset of spasms. However in a significant number of cases the aetiology remains unknown (i.e. idiopathic).

Two treatments are currently in widespread use i.e. vigabatrin and steroids. Steroids are either administered as ACTH or prednisolone. Steroids have been used in the treatment of seizure disorders since the late 1950's. They undoubtedly have a significant effect in reducing seizure frequency but side effects such as increased appetite, irritability and hypertension are common. There is no clear evidence about whether ACTH is preferable to prednisolone. The effectiveness of treatment has almost exclusively been measured in terms of reduction of seizure frequency and not in terms of improved psychomotor outcome. Vigabatrin has also recently been shown to reduce seizure frequency in patients with infantile spasms. Its side-effect profile appears better than that of steroids has been. It is gaining acceptance, although there are recent reports which suggest that it might affect visual fields in some adults. However it is not known whether it is better than steroids in treating infantile spasms and we don't know if either treatment might improve developmental outcome.

This trial will compare steroids and vigabatrin in the treatment of infantile spasms. It will assess outcome primarily in terms of reduction of seizure frequency and secondarily in terms of psychomotor development.

Trial design

UKISS is a national, multicentre, randomised, parallel-group open clinical trial. Patients will be allocated to one of two treatment groups:

1. Vigabatrin (50mg/kg increasing to a maximum of 150mg/kg per day)
2. Steroids. As ACTH gel is not available in the UK, we have substituted Synacthen Depot. Give either Synacthen Depot (0.5mg on alternate days increasing to 0.75mg on alternate days if necessary) or Prednisolone (40mg increasing to 60mg per day if necessary).

Patients will be stratified before entry according to sex, age and whether, at the time of randomisation, there is identifiable prior risk of developmental delay. Exclusions include tuberous sclerosis, proven at the time of randomisation.

Central randomisation will be by telephone call at which time the child will be registered into the trial. We will collect baseline information and allocate initial treatment. The initial treatment period for all three groups will be two weeks. Responders are defined as those in whom there is a total cessation of seizures for at least 48 hours up to and including the end of the 14th day of treatment.

Responders to vigabatrin are recommended to continue on a maintenance dose of the drug until aged 12 - 14 months unless that is not your normal practice. Responders to steroids (Synacthen Depot or prednisolone) will undergo a tapered withdrawal over 15 days, using prednisolone only. Responders who subsequently relapse will be treated by increasing the dose of vigabatrin to a maximum of 150mg/kg/day or in the case of steroids by giving a repeated dose. If this fails we recommend that the alternative therapy is tried (i.e. vigabatrin if steroids fail and steroids if vigabatrin fails).

Please note the precautions listed in the manufacturer's data sheet for Synacthen Depot. Synacthen Depot should only be administered *under medical supervision*. Previous hypersensitivity reaction (localised or generalised) to ACTH, Synacthen or Synacthen Depot is a contraindication to its use. It is also contraindicated in allergic disease. Hypersensitivity reactions generally occur within 30 minutes of administration (for which period direct observation of the child is recommended). However, the Committee on Safety of Medicines has not received any reports of anaphylaxis in children less than 5 years of age. Avoid live vaccines durings the period of treatment. Use with care in the presence of renal insufficiency and hypertension.

All patients will be seen as deemed necessary by their own consultant, but this must include a visit at two weeks to assess initial response to therapy and thereafter at 3 monthly intervals. Referring consultants will be asked to fill in standardised progress report forms and send them back to the trial centre in Bath after each of these consultations. The patient's psychomotor development will be assessed by a telephone questionnaire administered by the trial centre in Bath at 12 –14 months of age. Parents will be required to keep a diary until their child reaches 12 -14 months of age. There should be a daily entry for 28 days after the start of treatment and weekly after that until the 12-14 month development assessment. In those children still having any form of seizure at 12 -14 months, a daily entry will be obtained for the final week.

If you have any questions or concerns, or would like any further information on this study please to not hesitate to contact:

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

Trial Centre Tel: 01225 824206
Randomisation Tel: 01225 824490 *(8.30am to 6pm)*
(answer machine 6pm to 8.30am)
Fax: 01225 824206 or 01225 824212

24 hour number for hospital: 01225 428331

The United Kingdom Infantile Spasm Study

GP's information sheet

Infantile spasms (IS), also known as West syndrome were first described by Dr. West in 1841 who gave an account of them occurring in his own 4 month old son. They are a refractory seizure disorder with a high risk of a poor prognosis, including intractable epilepsy and severe developmental delay. The condition is relatively common with an incidence which may be as high as 1 in 2500 births. There is an association with a number of disorders. Some of the disorders, such as cerebral palsy or Down syndrome are known at the disease onset, whilst others, such as Tuberous Sclerosis or neuronal migration disorders are discovered on investigation after the onset of spasms. However in a significant number of cases the aetiology remains unknown (i.e. idiopathic).

Two treatments are currently in widespread use i.e. vigabatrin and steroids. Steroids are either administered as ACTH or prednisolone. Steroids have been used in the treatment of seizure disorders since the late 1950's. They undoubtedly have a significant effect in reducing seizure frequency but side effects such as increased appetite, irritability and hypertension are common. There is no clear evidence about whether ACTH is preferable to prednisolone. The effectiveness of treatment has almost exclusively been measured in terms of reduction of seizure frequency and not in terms of improved psychomotor outcome. Vigabatrin has also recently been shown to reduce seizure frequency in patients with infantile spasms. Its side-effect profile appears better than that of steroids has been. It is gaining acceptance, although there are recent reports which suggest that it might affect visual fields in some adults. However it is not known whether it is better than steroids in treating infantile spasms and we don't know if either treatment might improve developmental outcome.

This trial will compare steroids and vigabatrin in the treatment of infantile spasms. It will assess outcome primarily in terms of reduction of seizure frequency and secondarily in terms of psychomotor development.

Trial design

UKISS is a national, multicentre, randomised, parallel-group open clinical trial. Patients will be allocated to one of two treatment groups:

1. Vigabatrin (50mg/kg increasing to a maximum of 150mg/kg per day)
2. Steroids. As ACTH gel is not available in the UK, we have substituted Synacthen Depot. Give either Synacthen Depot (0.5mg on alternate days increasing to 0.75mg on alternate days if necessary) or Prednisolone (40mg increasing to 60mg per day if necessary).

Patients will be stratified before entry according to sex, age and whether, at the time of randomisation, there is identifiable prior risk of developmental delay. Exclusions include tuberous sclerosis, proven at the time of randomisation.

Central randomisation will be by telephone call at which time the child will be registered into the trial. We will collect baseline information and allocate initial treatment. The initial treatment period for all three groups will be two weeks. Responders are defined as those in whom there is a total cessation of seizures for at least 48 hours up to and including the end of the 14th day of treatment.

Responders to vigabatrin are recommended to continue on a maintenance dose of the drug until aged 12 - 14 months unless that is not your normal practice. Responders to steroids (Synacthen Depot or prednisolone) will undergo a tapered withdrawal over 15 days, using prednisolone only. Responders who subsequently relapse will be treated by increasing the dose of vigabatrin to a maximum of 150mg/kg/day or in the case of steroids by giving a repeated dose. If this fails we recommend that the alternative therapy is tried (i.e. vigabatrin if steroids fail and steroids if vigabatrin fails).

Please note the precautions listed in the manufacturer's data sheet for Synacthen Depot. Synacthen Depot should only be administered *under medical supervision*. Previous hypersensitivity reaction (localised or generalised) to ACTH, Synacthen or Synacthen Depot is a contraindication to its use. It is also contraindicated in allergic disease. Hypersensitivity reactions generally occur within 30 minutes of administration (for which period direct observation of the child is recommended). However, the Committee on Safety of Medicines has not received any reports of anaphylaxis in children less than 5 years of age. Avoid live vaccines durings the period of treatment. Use with care in the presence of renal insufficiency and hypertension.

All patients will be seen as deemed necessary by their own consultant, but this must include a visit at two weeks to assess initial response to therapy and thereafter at 3 monthly intervals. Referring consultants will be asked to fill in standardised progress report forms and send them back to the trial centre in Bath after each of these consultations. The patient's psychomotor development will be assessed by a telephone questionnaire administered by the trial centre in Bath at 12 –14 months of age. Parents will be required to keep a diary until their child reaches 12 -14 months of age. There should be a daily entry for 28 days after the start of treatment and weekly after that until the 12-14 month development assessment. In those children still having any form of seizure at 12 -14 months, a daily entry will be obtained for the final week.

If you have any questions or concerns, or would like any further information on this study please to not hesitate to contact:

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

Trial Centre Tel: 01225 824206
Randomisation Tel: 01225 824490 *(8.30am to 6pm)*
(answer machine 6pm to 8.30am)
Fax: 01225 824206 or 01225 824212

24 hour number for hospital: 01225 428331

Please send this sheet to the patient's general practitioner

The United Kingdom Infantile Spasm Study

Patient's information sheet

We would like to invite you to participate in a research study which aims to find the most effective way of treating infantile spasms. Your doctor will have given you some information about infantile spasms. These are a type of fit (or seizure or convulsion or epilepsy) which occur in babies or young infants. They are not very common and are often difficult to treat.

The fits consist of repeated attacks of sudden brief movements. The arms may be thrown in the air and then brought back like a cuddle. The child often bends double but may jerk backwards. Often lots of these fits occur one after another - which we call a batch of fits. There is then a gap with normal activity before the next batch. Occasionally the fits may occur individually. You may notice that they happen more often at certain times, for example, when your child is waking up or when he/she is tired.

It is often difficult to realise that the movements are fits. It may seem as if your child had colic or a normal startle reflex. It is therefore helpful for the doctors and nurses to see an attack. Your child will need an EEG (this may have happened already). An EEG measures the electrical activity of the brain. You will go with your child to a special quiet room. A technician will stick discs to your child's head. It does not hurt. Leads coming out from the discs will then measure the electrical activity of the brain. You will have to wash your child's hair afterwards.

Sometimes infantile spasms occur and we don't know why, but often there is a cause. To find the cause we will examine your child and do tests. These tests may be done even if your child does not enter the study.

1. We will look in your child's eyes with a special light (an ophthalmoscope). We often use eye drops which make the pupils bigger to make this easier.
2. We will look at your child's skin with a special ultraviolet light. This is completely harmless.
3. We will do a scan of the brain, which may require a short anaesthetic.
4. We will take a urine sample.
5. We will also take a sample of blood. The genes we inherit from our parents determine how we grow and develop. Sometimes genes also cause medical conditions and illnesses. We would like to find out if infantile spasms are an illness caused by genes. To do this we will need to send a small amount of blood to a laboratory in London where our colleagues will extract the genetic material from the blood. Any genetic material we extract from your child's blood will only be used for this study but, in line with recommendations of the Royal College of Pathologists, human DNA extracted from blood samples will be kept permanently at the laboratory in London.
6. Some blood may also be taken to measure steroid levels.

Once we are sure that these are infantile spasms we have to start treatment. We don't know that it is important that we start the medicines as quickly as possible, but in case it is important we will start the treatment as soon as we are certain that your child needs treatment.

Sometimes when these fits start your child's development may stop or you may find that they forget things that they have already learnt. Your doctor will talk to you in more detail about this as it varies greatly between children.

One of the most difficult problems with infantile spasms is the treatment. In the past anti-epileptic drugs have not been very good at stopping these types of fits. So instead different types of steroid (treatment by mouth or injection) have been used. Steroids will stop the spasms in just over half of patients. Unfortunately the fits can come back. One new anti-epileptic drug is now available which may be good at stopping the fits. It is called vigabatrin. We need to know if vigabatrin or one of the steroids is the best treatment.

Continued overleaf

We would like to ask you to take part in this study to find out which of the treatments is best. If we knew which was best, we would not be doing the study. If for any reason you would prefer not to take part in the study we will respect that decision and the care that your child receives will not be affected.

If you decide to take part in this study your child will given one of the following three drugs.

1. Synacthen Depot. This is given by injection on alternate days for two weeks. It tells your child's own body to make more natural steroids than usual.
2. Prednisolone. This is a type of natural steroid which is taken by mouth 3 or 4 times a day for two weeks.
3. Vigabatrin. This is an anti-epileptic drug which is taken by mouth 2 times a day for two weeks.

Your child will receive one of these drugs for two weeks. After 2 weeks your child will be seen by your doctor. If the fits have stopped then your child will:

- if on vigabatrin, continue on with the treatment until they are about 12 -14 months old if that is your doctor's normal practice.
- if on synacthen depot or prednisolone, be given oral prednisolone for 15 more days at a lower dose.

After 2 weeks, if the spasms have not stopped your child will be changed to a different treatment to see if that helps.

Your child will be seen by your doctor at least every three months (more often if necessary) to check progress. If there are problems with the spasms or the medicine please tell your doctor.

When your child is about 12 -14 months of age then we will contact you by phone to check on your child's progress. This will take between 15 and 30 minutes to complete.

During the study we will also ask you to fill in a diary. This will take just a couple of minutes a day. We will ask you to mark if your child has had any fits that day or any other illness. We will ask you to return the diary at the end of the study, but you may keep a copy if you want. It will be a permanent record of your child's progress.

If we do not do this study we will never learn which treatment is best. If we knew now which treatment was best then we would not be doing the study. It will take all, or nearly all, of the children in the UK to agree to the study for about 18 months before we expect to know which is the best treatment. Then we can give the best treatment to all children with infantile spasms. This is the usual way doctors study drugs to see which ones are best.

The information collected on your child will be kept by the doctors in charge of the study. They will keep it safe in locked filing cabinets. Some information will be kept on computer: it will be protected by a secret password.

If you want to ask about the information or to ask any other questions ask your local specialist. We will send you a news letter every few months, this will tell you how the study is going.

If you need to, you can contact your specialist:

His / Her name is: .....

Address: .....

.....

.....

.....

Telephone No: .....

If you need to you can also contact the doctor in charge of the study:

Prof J. Osborne
The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG
Tel: 01225 824206 ***but please talk to your local specialist first.***

The United Kingdom Infantile Spasm Study

Patient information sheet — Prednisolone

Dear parent / guardian,

Thank you for participating in the UKISS study. Your child may be chosen to receive prednisolone either as their first drug in this study or because vigabatrin did not stop their spasms. Hopefully this information sheet will answer any questions you have about prednisolone and its use. If you have any other questions or there is anything that you do not understand ask your doctor now.

What is prednisolone?

Prednisolone is the chemical name for a type of steroid that our bodies produce naturally. It is also available as a medicine. It is made by a drug company (Glaxo) who call their brand of the drug Prednesol (in the same way that Nestle call their coffee Nescafe).

How do I give it?

It comes in tablet form. Each small pink tablet contains 5mg prednisolone. It is taken by mouth either 3 or 4 times a day. They can either be crushed and sprinkled on food or can be dissolved in water (or squash). They may be taken before, during or after meals.

How much do I give?

For the first week of treatment you will give 10mg four times a day (2 tablets four times a day). If at the end of the first week your child's spasms have not stopped then your doctor will tell you to increase the dose to 20mg three times a day (4 tablets three times a day). After the two weeks you will need to reduce the dose of prednisolone. Your doctor will explain how to do this. The amount of medicine needed does not depend on your child's weight or age.

If the spasms start again you doctor may ask you to repeat the course of steroids.

If your child accidentally takes too much Prednesol, tell your doctor immediately or go to your nearest casualty department.

If you forget to give a dose give another as soon as you remember, unless it is almost time for their next dose, then go on as before.

Are there any side effects?

As with all medicines some side effects may occur. The most common side effects of prednisolone are irritability and changes in sleeping. These will improve once the steroids are stopped.

Your doctor (either your GP or a doctor from the hospital) will need to see your child once a week to check their blood pressure and urine.

Because we only use the steroids for a short time, they do not cause long lasting effects. For example, your child will not stop growing as an effect of the steroids.

What do I do if my child has any side effects?

Contact your doctor (GP) immediately. He/she will advise you on whether to continue the prednisolone or whether you need to stop the prednisolone. If you have to stop the prednisolone you must see your child's paediatrician as soon as possible so he/she can give you some different medicine to stop the spasms. You should also write down the problem in your 'fit diary'.

What do I do if my child becomes ill?

If your child becomes unwell in any way or if you have any concerns you should contact your doctor (GP) immediately. If your child develops chickenpox or is in contact with another child who develops chickenpox you must contact your doctor immediately.

Immunisations:

Your child should not have their immunisations (vaccinations, jabs) whilst they are on their steroids. They should have their immunisations once they have completely finished their course of steroids.

The United Kingdom Infantile Spasm Study

Patient information sheet — Vigabatrin

Dear parent / guardian,

Thank you for participating in the UKISS study. Your child may be chosen to receive vigabatrin either as their first drug in this study or because the steroid treatment did not stop their spasms. Hopefully this information sheet will answer any questions you have about vigabatrin and its use. If you have any other questions or there is anything that you do not understand then ask your doctor now.

What is vigabatrin?

Vigabatrin is the chemical name of the drug. It is made by a drug company (Hoechst Marion Roussel) who call their brand of the drug Sabril (in the same way that Nestle call their coffee Nescafe).

How do I give it?

It comes in sachets. Each sachet contains 500 mg vigabatrin as a white powder. Do not open the sachet until it is time to give the medicine. It is taken by mouth (orally) two times a day. It can be sprinkled on food or dissolved in a drink (for example water, squash, milk, tea). It may be taken before, during or after meals.

How much do I give?

Your doctor will work out how much of the medicine your child has to take. The amount needed depends on how much your child weighs. We will build up the amount of vigabatrin your child takes over the first two days. After four days we may increase the dose further if your child's spasms have not stopped. It may also be necessary to increase the dose later in the trial if the spasms start again or as your child increases in weight. You do not need to worry about this, your doctor will work out how much medicine is needed and will tell you how much to give to your child.

If your child accidentally takes too much vigabatrin, tell your doctor immediately or go to your nearest casualty department.

If you forget to give a dose give another as soon as you remember, unless it is almost time for their next dose then go on as before.

Are there any side effects?

As with all medicines some side effects may occur. The most common side effect of vigabatrin is sleepiness. This usually wears off after a few days. Occasionally your child may vomit (be sick). Recently, some adults treated with vigabatrin have been found to have visual field defects (difficulty in seeing around the edge of their normal area of vision). This may be more likely if treatment continues for a long time Other side effects are very rare.

What do I do if my child has any side effects?

Contact your doctor (GP) immediately. He/she will advise you on whether to continue the vigabatrin or whether you need to stop the vigabatrin. If you have to stop the vigabatrin you must see your child's paediatrician as soon as possible so he/she can give you some different medicine to stop the spasms. You should also write down the problem in your 'fit diary'.

What do I do if my child becomes ill?

If your child becomes unwell in any way or if you have any concerns you should contact your doctor (GP) immediately.

The United Kingdom Infantile Spasm Study

Patient Information Sheet - Synacthen Depot

Dear parent / guardian,

Thank you for participating in the UKISS study. Your child may be chosen to receive Synacthen Depot either as their first drug in this study or because vigabatrin did not stop their spasms. Hopefully this information sheet will answer any questions you have about Synacthen Depot and its use. If you have any other questions or there is anything that you do not understand ask your doctor now.

What is Synacthen Depot?

Synacthen Depot is the trade name for a manufactured medicine which is a type of hormone our bodies produce naturally (a type of adrenocorticotrophic hormone). This hormone causes the production of natural steroids by the body. It is made by a drug company who call their brand of the drug Synacthen Depot (in the same way that Nestle call their coffee Nescafe).

How will it be given?

It is given as an intramuscular (into the muscle - usually the top of the leg) injection, on alternate days by a trained medical person (your doctor or nurse).

Are there any side effects?

As with all medicines some side effects may occur. The most common side effects are irritability and changes in sleeping. These will improve once the steroids are stopped.

Your doctor will ask you about any known allergies because Synacthen Depot can upset children with allergies.

Your doctor (either your GP or a doctor from the hospital) will need to see your child once a week to check their blood pressure and urine.

Because we only use the steroids for a short time, they do not cause long lasting effects. For example, your child will not stop growing as an effect of the steroids.

What do I do if my child has any side effects?

Contact your doctor (GP) immediately. If you have to stop the Synacthen Depot you must see your child's paediatrician as soon as possible so he/she can give you some different medicine to try to stop the spasms. You should also write down the problem in your 'fit diary'

What do I do if my child becomes ill?

If your child becomes unwell in any way or if you have any concerns you should contact your doctor (GP) immediately. If your child develops chickenpox or is in contact with another child who develops chickenpox you must contact your doctor immediately.

Immunisations:

Your child should not have their immunisations (vaccinations, jabs) whilst they are on their steroids. They should have their immunisations once they have completely finished their course of steroids.

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The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG
Tel/Fax: 01225 824206

The United Kingdom Infantile Spasm Study

Consent Check List for the UKISS Drug Trial

This check list must be completed prior to randomisation and kept in this folder

Child's full name (BLOCK CAPITALS): .....

Date of birth: Day/..... Month/..... Year/.....

Please tick ✓ ONE box on EACH line

1. Have you given the parents / guardians an oral explanation of the proposed research project? Yes ☐ No ☐

2. Did your oral explanation to the parents / guardians include:
   - that this is a research project? Yes ☐ No ☐
   - participation is voluntary? Yes ☐ No ☐
   - the aims of the project? Yes ☐ No ☐
   - the duration of the subject involvement? Yes ☐ No ☐
   - the nature of the drugs being tested? Yes ☐ No ☐
   - what risks, inconvenience, discomfort or distress may be reasonably anticipated? Yes ☐ No ☐
   - that a refusal to participate may be given without reasons and will not affect the care which will be given to the child? Yes ☐ No ☐
   - that the subject may be withdrawn from the study if the investigating paediatrician considers this is necessary in the best interests of the child? Yes ☐ No ☐
   - that personal information may be scrutinised by properly authorised people, but all personal information will be treated as strictly confidential and will not be made publicly available? Yes ☐ No ☐
   - that the information generated by the study may be published but that no details will be divulged from which the subject could be identified? Yes ☐ No ☐
   - whom to contact in an emergency? Yes ☐ No ☐

3. Have you given the information sheet to the parents/guardians? Yes ☐ No ☐

4. Have you told the parents/guardians that they will be kept informed of relevant information which becomes available during the course of the study? Yes ☐ No ☐

5. Have you allowed the parents / guardians sufficient time to consider the matter on their own, to discuss with others if wished, or to ask you questions? Yes ☐ No ☐

6. In your opinion, have the parents / guardians understood and consented for their child to take part in this research? Yes ☐ No ☐

Name of investigator obtaining consent

Signed: .....

PRINT name: .....

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The United Kingdom Infantile Spasm Study

FORM A: CONSENT FOR DRUG TRIAL

CONSENT BY THE PARENT / GUARDIAN

Patients full name (BLOCK CAPITALS): .....

Date of birth: Day/ ..... Month/ ..... Year/ .....

Address: .....

.....

I hereby fully and freely consent to allow my child to participate in the UKISS trial.
(Please tick ✓ appropriate boxes)

- Have you read the patient information sheet? ..... Yes ☐ No ☐
- Have you had an opportunity to ask questions and discuss this study? ..... Yes ☐ No ☐
- Have you received satisfactory answers to all your questions? ..... Yes ☐ No ☐
- Have you received enough information about the study? ..... Yes ☐ No ☐
- I agree that my general practitioner and hospital consultant are notified of my child's participation in the trial and that they may release information on my child's past medical history.
- I understand and acknowledge that the trial is designed to promote medical knowledge.
- I understand that some information will be kept on computer in password protected files.
- I understand that I may withdraw my consent at any stage in the trial. I understand that I do not have to give a reason for withdrawing. I understand that this would not affect the care that my child receives.
- I acknowledge the purpose of the trial and the risks involved from the procedures that may be undertaken. The nature and purpose of the trial has been given to me in an information sheet and has been explained to me by:

  .....

  and I have discussed these matters with him/her.

Signed: ..... Date: .....

Name (PRINT): .....

Witness (signature): .....

Name (PRINT): .....

Parent / Guardian *(Please ring as appropriate)*

DECLARATION BY THE INVESTIGATOR

I confirm that I have provided an information sheet and explained the nature and effect of the trial to the parent / guardian and that consent has been given freely and voluntarily.

Signed: .....

Name (PRINT): .....

Status: ..... Hospital name: .....

I understand that some information will be kept on computer in password protected files.

Please return a photocopy of this form to: The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

The United Kingdom Infantile Spasm Study

FORM B: CONSENT FOR EPIDEMIOLOGY STUDY

CONSENT BY THE PARENT / GUARDIAN

Patients full name (BLOCK CAPITALS): .....

Date of birth: Day/..... Month/..... Year/.....

Address: .....

.....

I have chosen **not** to allow my child to participate in the UKISS drug trial. However in order to allow the investigators to learn more about infantile spasms I agree to allow my clinician to give the investigators the following information about my child:

1. Details about my child's spasms, for example what age they started, how many occur in a day and which muscles they involve.
2. Details about my child's development.
3. Details about my child's past medical history.
4. Details about my child's examination.
5. Results of any tests performed on my child.

I understand that I do not have to consent to release of this information and that if I do not consent it will not affect the care that my child receives.

I understand that some information will be kept on computer in password protected files.

Signed: ..... Parent/Guardian
(delete as appropriate)

Name (PRINT): ..... Date: .....

Witness (Signature): .....

Name (PRINT): .....

DECLARATION BY THE INVESTIGATOR

I confirm that I have provided an information sheet and explained the nature and effect of the trial to the parent / guardian and that consent has been given freely and voluntarily.

Signed: .....

Name (PRINT): .....

Status: .....

Hospital name: .....

I undersand that some information will be kept on computer in password protected files.

Pleasereturn a photocopy of this form to: The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

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The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG
Tel/Fax: 01225 824206

UKISS
The United Kingdom Infantile Spasm Study

FORM ONE – Notification

You will need to have this completed questionnaire available when you phone the randomisation centre for patient entry into the UKISS trial. This form should be completed even if the parents decline to participate in the drug trial or the epidemiology study. We wish to know how many patients have been excluded from this trial so that we may compare our study population to the whole population of infants with infantile spasms.

If in neither study (i.e. No Consent) please photocopy BOTH sides of this form BEFORE use and Tick (✓) here ☐ on photocopy

Telephone 01225 824206 for advice / with queries 8.30am to 6pm weekdays

Today's date: Day/ Month/ Year/ Child's initials:

Child's date of birth: Day/ Month/ Year/

1. Doctors details

Name of consultant (PRINT): Name of GP:

Name of enrolling doctor (PRINT): GP address:

Grade of enrolling doctor (PRINT):

Hospital address(PRINT):

Hospital/Dept tel no: (if known) GP tel no.:

2. Exclusion criteria for drug trial (see protocol for details) Please tick ✓ ONE box on EACH line

Please complete EVEN if enrolment in Drug Trial is not being considered

- Is the patient aged below 2 months? Yes ☐ No ☐
- Is the patient aged over one year? Yes ☐ No ☐
- Is the patient known to have or be at high risk of having tuberous sclerosis? Yes ☐ No ☐
- Has the patient been treated with vigabatrin or steroids in the past 28 days? Yes ☐ No ☐
- Is there any contraindication to vigabatrin, prednisolone or Synacthen Depot? Yes ☐ No ☐
- Has the patient previously been treated for infantile spasms? Yes ☐ No ☐
- Does the infant have a lethal or potentially lethal condition? Yes ☐ No ☐
- Is the patient expected to leave the UK within one month of randomisation? Yes ☐ No ☐
- Is the infant enrolled in a concurrent trial that either uses therapy that might affect the outcome measures of the UKISS trial or one that is time/effort consuming for the patients/guardians or the infants' medical practitioners? Yes ☐ No ☐
- Are the parents or guardian unable to give informed, signed, consent? Yes ☐ No ☐
- Are the parents or guardian unable to know when the spasms stop? (to the nearest whole day) Yes ☐ No ☐

If the answer to any of the above questions is **YES,** then the patient is **excluded** from the drug tria, **but please request consent for the Epidemiology Study** and continue overleaf.

Please turn over

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Please tick ✓ **one** box on each line

3.	Sex of patient		Male ☐	Female ☐
4.	Does the child have a known proven chromosomal abnormality?	Yes ☐	No ☐	
5.	Does the child have a known proven syndrome?	Yes ☐	No ☐	
6.	Did the child have a diagnosis of cerebral palsy made prior to the onset of the spasms?	Yes ☐	No ☐	
7.	Did the child have neonatal encephalopathy with seizures?	Yes ☐	No ☐	
8.	Was the child already diagnosed as having abnormal development before the onset of spasms *(this diagnosis must have been made BEFORE the onset of spasms, by a doctor or health visitor)*?	Yes ☐	No ☐	

9. Current medications

Drug	Total Daily Dose

10. Current weight _____:_____ kg

If this patient is to be included in the Drug Trial, please complete Consent Form A

Please return a photocopy of this form to:

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

Thank you very much for your help

01367

The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG
Tel/Fax: 01225 824206

The United Kingdom Infantile Spasm Study

FORM TWO – Enrolment in DRUG TRIAL

Patient's details

Patient's name (PRINT):

Date of birth: Day/ Month/ Year/

Hospital number:

Address:

Hospital name:

If the child is to be entered into the drug trial please phone the randomisation centre between 8.30 and 18.00 (Monday – Friday) on Tel: 01225 824490 and then complete this form.

Randomised to receive: vigabatrin ☐ Synacthen depot ☐ prednisolone ☐ *(please tick ✓)*

Study number: ☐ (Please put this number on the front of the **14 day Assessment Form** and the **Patient's Diary NOW**. The Patient's Diary is inside the back cover)

Date of randomisation: Day/ Month/ Year/ Time of randomisation : (24 hour clock)

Discussed with: at the Trial Centre

1. EEG

a. Has a standard EEG been performed? Yes ☐ No ☐

If **YES**, what was the result? Normal Yes ☐ No ☐

Hypsarrhythmia Yes ☐ No ☐

Other Yes ☐ No ☐

please specify:

b. Has a sleep EEG been performed? Yes ☐ No ☐

If **YES**, what was the result? Normal Yes ☐ No ☐

Hypsarrhythmia Yes ☐ No ☐

Other Yes ☐ No ☐

please specify:

c. Has a video EEG been performed? Yes ☐ No ☐

If **YES**, what was the result? Normal Yes ☐ No ☐

Hypsarrhythmia Yes ☐ No ☐

Other Yes ☐ No ☐

please specify:

Please attach a photocopy of any EEG report(s)

2. Diagnosis

Is there a known underlying diagnosis or cause for the spasms? Yes ☐ No ☐

If **YES**, *please specify:*

3. Since the onset of the spasms

a. (i) Has there been arrest of development? Yes ☐ No ☐ Don't know ☐

(ii) If **Yes,** did this coincide with the start of the spasms? Yes ☐ No ☐ Don't know ☐

b. (i) Has their been regression of development? Yes ☐ No ☐ Don't know ☐

(ii) If **Yes,** did this coincide with the start of the spasms? Yes ☐ No ☐ Don't know ☐

c. UKISS Development Chart

Please fill in this chart when the child is entered into the trial. In order to get some indication of whether there has been arrest of development or regression before the onset of treatment, please respond to the questions for the **best ever development** to date (in the column headed 'Best ever') and the **current developmental attainment** (in the column headed 'Current'). (Please tick ✓)

Date of assessment Day/ ..... Month/ ..... Year/ .....

Developmental milestone	**Best ever**	**Current**
Hand regard: Does the child focus on and look attentively at the hands and fingers?		
Laugh: Does the child respond at times by laughing loudly - a 'belly laugh'?		
Play with feet: Does the child focus on, grasp, and play with the feet?		
Grasps an object: Does the child grasp a small object within reach when sitting with support (palmar grasp is sufficient)?		
Transfers an object: Does the child transfer a small object from one hand to another deliberately?		
Sits unsupported: Does the child sit by itself on a flat surface?		
Permanency: Does the child know where to look for an object that has fallen out of view?		
Crawls: Can the child crawl around on all fours?		
Gives an object: Does the child hand an object to someone on request (when prompted by gesture and voice)?		

When completed please send a photocopy of this form to the Trial Centre:

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

(as in Action Plan 1 or 2)

Thank you very much for your help

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Combe Park
Bath BA1 3NG
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The United Kingdom Infantile Spasm Study

FORM THREE — Enrolment in EPIDEMIOLOGY STUDY

Please complete this form for ANY infant diagnosed as having infantile spasms who has been excluded for whatever reason from the treatment component of this study. The information on this form is ESSENTIAL provided the parents/guardians have given consent for the epidemiology study.

Essential information

Patient's name (PRINT): .....

Date of birth: Day/ ..... Month/ ..... Year/ .....

Hospital number: .....

Address(PRINT): .....

.....

.....

Hospital name: .....

Study number: ☐ (Please put this number on the front of the **14 day Assessment Form** and the **Patient's Diary NOW**. The Patient's Diary is inside the back cover)

1. Reason for non-entry into drug trial if other than exclusion:

a. Non-participating centre — Yes ☐ No ☐

b. Unable to get EEG within 72 hours and you don't normally treat before EEG result known — Yes ☐ No ☐

c. EEG and sleep EEG normal — Yes ☐ No ☐

d. Parents / guardians declined to take part — Yes ☐ No ☐

e. Other (please state): .....

2. Non-randomised treatment

a. Which drug are you intending to use as primary treatment of the infantile spasms?

Drug	Total Daily Dose

b. Any comments on intended treatment:

(please state): .....

.....

c. Please state date: Day/ ..... Month/ ..... Year/ .....

and approximate time ..... : ..... (24 hour clock) that this treatment decision was made

Please turn over

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3. EEG

a. Has a standard EEG been performed? Yes ☐ No ☐

If **YES**, what was the result? Normal Yes ☐ No ☐

Hypsarrhythmia Yes ☐ No ☐

Other Yes ☐ No ☐

please specify: .....

b. Has a sleep EEG been performed? Yes ☐ No ☐

If **YES**, what was the result? Normal Yes ☐ No ☐

Hypsarrhythmia Yes ☐ No ☐

Other Yes ☐ No ☐

please specify: .....

c. Has a video EEG been performed? Yes ☐ No ☐

If **YES**, what was the result? Normal Yes ☐ No ☐

Hypsarrhythmia Yes ☐ No ☐

Other Yes ☐ No ☐

please specify: .....

Please attach a photocopy of any EEG report(s)

4. Diagnosis

Is there a known underlying diagnosis or cause for the spasms? Yes ☐ No ☐

If **YES**, *please specify:* .....

5. Since the onset of the spasms

a. (i) Has there been arrest of development? Yes ☐ No ☐ Don't know ☐

(ii) If **YES,** did this coincide with the start of the spasms? Yes ☐ No ☐ Don't know ☐

b. (i) Has their been regression of development? Yes ☐ No ☐ Don't know ☐

(ii) If **YES,** did this coincide with the start of the spasms? Yes ☐ No ☐ Don't know ☐

c. UKISS Development Chart

Please fill in this chart when the child is entered into the trial. In order to get some indication of whether there has been arrest of development or regression before the onset of treatment, please respond to the questions for the **best ever development** to date (in the column headed 'Best ever') and the **current developmental attainment** (in the column headed 'Current'). (Please tick)

Date of assessment Day/ ..... Month/ ..... Year/ .....

Developmental milestone	**Best ever**	**Current**
Hand regard: Does the child focus on and look attentively at the hands and fingers?		
Laugh: Does the child respond at times by laughing loudly - a 'belly laugh'?		
Play with feet: Does the child focus on, grasp, and play with the feet?		
Grasps an object: Does the child grasp a small object within reach when sitting with support (palmar grasp is sufficient)?		
Transfers an object: Does the child transfer a small object from one hand to another deliberately?		
Sits unsupported: Does the child sit by itself on a flat surface?		
Permanency: Does the child know where to look for an object that has fallen out of view?		
Crawls: Can the child crawl around on all fours?		
Gives an object: Does the child hand an object to someone on request (when prompted by gesture and voice)?		

Please return a photocopy of this form to:

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The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

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The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG
Tel/Fax: 01225 824206

The United Kingdom Infantile Spasm Study

FORM FOUR — DRUG TRIAL & EPIDEMIOLOGY Assessment at 14 Days

This form should be completed when the child is reviewed at the end of the initial two weeks of therapy. This assessment should take place as close to, but **NOT BEFORE 14** completed days of the initial therapy.

Date of assessment: Day/..... Month/..... Year/.....

Patient details:

Name (PRINT): .....

Date of birth: Day/..... Month/..... Year/.....

Study number: ☐ (when completing put number on the front of the **3 Monthly Assessment Form**)

1. The spasms

a. (i) Age at **onset** of the spasms: ..... Is the exact date known? Yes ☐ No ☐

(ii) If **YES,** specify date: day/..... month/..... year/.....

(iii) If **NO**, is the age accurate to the nearest: week ☐ month ☐

b. Date of **diagnosis** of the spasms day/..... month/..... year/.....

c. (i) Has there been complete cessation of spasms for 48 hours since commencing treatment? Yes ☐ No ☐

(ii) If **YES**, date of last spasm ? day/..... month/..... year/.....

d. What date did treatment commence? day/..... month/..... year/.....

e. (i) Has there been a relapse since? Yes ☐ No ☐

(ii) If **YES**, have spasms stopped again for 48 hours ? Yes ☐ No ☐

2. Pregnancy

a. (i) Were there any maternal problems/illnesses during pregnancy? Yes ☐ No ☐

(ii) If **YES**, what were they? .....

3. Birth history

a. Gestation at delivery: ...../40

b. (Please tick ✓ boxes) (i) vaginal ☐ (ii) forceps ☐ (iii) ventouse ☐

(iv) planned section ☐ (v) emergency section ☐ (vi) breech ☐ (vii) cephalic ☐

c. Birth weight: ..... grams

d. Apgars (if known): (i) ..... @1 (ii) ..... @5 (iii) ..... @10

e. Head circumference at birth: .... cm

f. History of neonatal problems .....

4. Any other past medical illnesses / operations

Please turn over

5. Any preceding fits and their treatment

6. Any family history of epilepsy or relevant medical conditions in first degree relatives.

(Please indicate how many first degree relatives affected/unaffected.)

7. Drug history

Medication between day 1 and day 14 (including medication for infantile spasms):

	(i) Drug	(ii) Single dose	(iii) No of times given (e.g. bd, tds)	(iv) Days on which the drug was given (eg days 1-7)
a.				
b.				
c.				
d.				
e.				
f.				
g.				

Proposed changes after day 14 to current medication (if any) and reasons:

h.

8. Clinically important adverse events

a. Have the parents/guardians reported any clinically important adverse events (symptoms, illnesses or surgery) regardless of whether related to the treatment(s) given? **Yes** ☐ **No** ☐

b. If **Yes**, please complete the details in the table below.
If you think that the adverse event is attributable to the trial drug, please place an asterisk (*) in the first box.

	Adverse event	Date of onset	Hospitalisation		Action taken				Clinical outcome		
			Yes	No	None	Treatment			Recovered	Not recovered	Unknown
						Reduced	Stopped	Stopped temporarily			
*											

Any life-threatening adverse event or any event requiring withdrawal of treatment should be reported to the Trial Centre IMMEDIATELY.

Please continue

9. Neurological assessment

a. (i) Was the neurological examination of the infant normal? Yes ☐ No ☐

(ii) If **NO**, please describe any findings below e.g. hypotonia, spasticity:

.....

.....

b. (i) Were the fundi examined with an opthalmoscope? Yes ☐ No ☐

(ii) If **YES**, were there any abnormal findings?

.....

c. (i) Was a Woods light examination performed? Yes ☐ No ☐

(ii) If **YES**, were there any abnormal findings?

.....

d. Please list any other neurocutanous findings

.....

e. (i) Are there any dysmorphic features? Yes ☐ No ☐

(ii) If **YES**, please list: .....

.....

f. (i) Current weight: .... kg (ii) Current head (occipitofrontal) circumference: .... cm

10. Blood pressure

a. Has BP (either systolic **or** diastolic) risen above (Please tick ✓ one box only)? (i) $^{110}/_{80}$ ☐ (ii) $^{120}/_{90}$ ☐ (iii) No ☐

b. Have antihypertensive drugs been started? Yes ☐ No ☐

c. Did the drug treatment of infantile spasms have to be stopped as a result of the hypertension? Yes ☐ No ☐

11. Urine analysis

a. (i) Has urine analysis been performed? Yes ☐ No ☐

(ii) If **YES**, was glycosuria recorded? Yes ☐ No ☐

(iii) If **YES**, was any treatment required? Yes ☐ No ☐

b. Did treatment have to be stopped as a result of diabetes? Yes ☐ No ☐

12. Investigations performed

Please indicate whether or not the following investigations have been performed on the patient. If they have then where possible please can you either enclose copies of the reports or fill in the result on this form. If they have not had the investigation, please indicate whether it is planned in the future or give the reason for it not being done.

a. (i) Was EEG performed at 14 days *(the time of this assessment)* Yes ☐ No ☐

(ii) If **YES**, Date: .....

(iii) Result *(attach photocopy of report if abnormal)* Normal ☐ Hypsarrhythmia ☐ Other ☐

(iv) *Comments* .....

(v) If **NOT** done, is it planned for the future? Yes ☐ No ☐

(vi) If **NOT** planned, *please specify reason:* .....

b. (i) Was an MRI of the brain performed? Yes ☐ No ☐

(ii) If **YES**, result *(attach photocopy of report if abnormal)* Normal ☐ Abnormal ☐

(iii) *Comments* .....

(iv) If **NOT** done, is it planned for the future? Yes ☐ No ☐

(v) If **NOT** planned, *please specify reason (e.g. CT done)* .....

Please turn over 13

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The United Kingdom Infantile Spasm Study

The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG
Tel/Fax: 01225 824206

FORM 6(a) – THREE MONTHLY ASSESSMENT FORM (DRUG TRIAL)

This form should be completed when the child is reviewed **THREE** months after enrolment into the trial (unless preceded by final assessment).

Patient details:

Name (BLOCK CAPITALS): .....

Date of birth: Day/..... Month/..... Year/.....

Study number: ..... **Please now put Study Number on next Assessment Form**

Today's date: Day/..... Month/..... Year/.....

Date of last Assessment: Day/..... Month/..... Year/.....

1. Effect of the therapy on the spasms (not other seizure types)

a. Has the child had any spasms since the last assessment? Yes ☐ No ☐

b. Have any changes been made to their treatment? Yes ☐ No ☐

c. If **YES**, please state those changes and when were they made?

.....

.....

.....

.....

2. EEG

a. Any further EEG? Yes ☐ No ☐

b. Date: Day/..... Month/..... Year/.....

c. Result: Normal ☐ Abnormal ☐

(Please attach a photocopy of any abnormal result)

3. Epileptic Seizures

a. Has the child had any other type of epileptic seizure since last assessment? Yes ☐ No ☐

4. Drug history at time of this assessment

(please record all drugs currently being taken)

	Drug (i)	Total Daily Dose (ii)
a.	.....	.....
b.	.....	.....
c.	.....	.....
d.	.....	.....

5. Clinically important adverse events

a. Have the parents/guardians reported any clinically important adverse events (symptoms, illnesses or surgery) regardless of whether related to the treatment(s) given?

Yes ☐ No ☐

b. If **Yes**, please complete the details in the table below.
(If you think that the adverse event is attributable to the trial drug, please place an asterisk (*) in the first box.)

	Adverse event	Date of onset	Hospitalisation		Action taken				Clinical outcome		
			Yes	No	None	Treatment			Recovered	Not recovered	Unknown
						Reduced	Stopped	Stopped temporarily			
*											

6. Investigations performed to find underlying cause

Have any further investigations been performed since the child's last review?

Please list and give the results where available

a) .....

b) .....

c) .....

d) .....

e) .....

7. Any other comments

.....

.....

.....

.....

.....

Please send a photocopy of this completed form to the Trial Centre (as in Action Plan 1 or 2)

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

Thank you very much for your help

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The United Kingdom Infantile Spasm Study

The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG
Tel/Fax: 01225 824206

FORM 6(b) -- THREE MONTHLY ASSESSMENT FORM (DRUG TRIAL)

This form should be completed when the child is reviewed **SIX** months after enrolment into the trial (unless preceded by final assessment).

Patient details:

Name (BLOCK CAPITALS): .....

Date of birth: Day/..... Month/..... Year/.....

Study number: ☐ **Please now put Study Number on next Assessment Form**

Today's date: Day/..... Month/..... Year/.....

Date of last Assessment: Day/..... Month/..... Year/.....

1. Effect of the therapy on the spasms (not other seizure types)

a. Has the child had any spasms since the last assessment? Yes ☐ No ☐

b. Have any changes been made to their treatment? Yes ☐ No ☐

c. If **YES**, please state those changes and when were they made?

.....

.....

.....

.....

2. EEG

a. Any further EEG? Yes ☐ No ☐

b. Date: Day/..... Month/..... Year/.....

c. Result: Normal ☐ Abnormal ☐

(Please attach a photocopy of any abnormal result)

3. Epileptic Seizures

a. Has the child had any other type of epileptic seizure since last assessment? Yes ☐ No ☐

4. Drug history at time of this assessment

(please record all drugs currently being taken)

	Drug (i)	Total Daily Dose (ii)
a.	.....	.....
b.	.....	.....
c.	.....	.....
d.	.....	.....

5. Clinically important adverse events

a. Have the parents/guardians reported any clinically important adverse events (symptoms, illnesses or surgery) regardless of whether related to the treatment(s) given?

Yes ☐ No ☐

b. If **Yes**, please complete the details in the table below.
(If you think that the adverse event is attributable to the trial drug, please place an asterisk (*) in the first box.)

	Adverse event	Date of onset	Hospitalisation			Action taken			Clinical outcome		
			Yes	No	None	Treatment			Recovered	Not recovered	Unknown
						Reduced	Stopped	Stopped temporarily			
*											

6. Investigations performed to find underlying cause

Have any further investigations been performed since the child's last review?

Please list and give the results where available

a) .....

b) .....

c) .....

d) .....

e) .....

7. Any other comments

.....

.....

.....

.....

Please send a photocopy of this completed form to the Trial Centre (as in Action Plan 1 or 2)

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

Thank you very much for your help

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The United Kingdom Infantile Spasm Study

FORM 6(c) -- THREE MONTHLY ASSESSMENT FORM (DRUG TRIAL)

This form should be completed when the child is reviewed **NINE** months after enrolment into the trial (unless preceded by final assessment).

Patient details:

Name (BLOCK CAPITALS): .....

Date of birth: Day/..... Month/..... Year/.....

Study number: ☐ **Please now put Trial Number on Final Assessment Form**

Today's date: Day/..... Month/..... Year/.....

Date of last Assessment: Day/..... Month/..... Year/.....

1. Effect of the therapy on the spasms (not other seizure types)

a. Has the child had any spasms since the last assessment? Yes ☐ No ☐

b. Have any changes been made to their treatment? Yes ☐ No ☐

c. If **YES**, please state those changes and when were they made?

.....

.....

2. EEG

a. Any further EEG? Yes ☐ No ☐

b. Date: Day/..... Month/..... Year/.....

c. Result: Normal ☐ Abnormal ☐

(Please attach a photocopy of any abnormal result)

3. Seizures

a. Has the child had any other type of seizure since last assessment? Yes ☐ No ☐

4. Drug history at time of this assessment

(please record all drugs currently being taken)

	Drug (i)	Total Daily Dose (ii)
a.	.....	.....
b.	.....	.....
c.	.....	.....
d.	.....	.....

Please turn over

5. Clinically important adverse events

a. Have the parents/guardians reported any clinically important adverse events (symptoms, illnesses or surgery), regardless of whether related to the treatment(s) given?

Yes ☐ No ☐

b. If **Yes**, please complete the details in the table below.
(If you think that the adverse event is attributable to the trial drug, please place an asterisk (*) in the first box.)

Adverse event	Date of onset	Hospitalisation		Action taken				Clinical outcome		
		Yes	No	None	Treatment			Recovered	Not recovered	Urknown
					Reduced	Stopped	Stopped temporarily			
*										

6. Investigations performed to find underlying cause

Have any further investigations been performed since the child's last review?

Please list and give the results where available

a) .....

b) .....

c) .....

d) .....

e) .....

7. Any other comments

.....

.....

.....

.....

.....

Please send a photocopy of this completed form to the Trial Centre (as in Action Plan 1 or 2)

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG

Thank you very much for your help

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The United Kingdom Infantile Spasm Study

FORM SEVEN — FINAL ASSESSMENT AT 12 TO 14 MONTHS OF AGE (Drug Trial and Epidemiology Study)

This form should be completed when the child is reviewed between the ages of 12 and 14 months.

Patient details:

Name (PRINT): .....

Date of birth: Day/ ..... Month/ ..... Year/ .....

Address: .....
(if changed) .....

.....

Home telephone number: .....

Study number:

Date of assessment Day/ ..... Month/ ..... Year/ .....

1. Effect of the therapy on the spasms *(not other seizure types)*

a. Has the child had any spasms since the last assessment? Yes ☐ No ☐

b. Have any changes been made to their treatment? Yes ☐ No ☐

c. If **YES**, what were those changes and when were they made?

.....

.....

2. EEG?

a. Any recent EEG? Yes ☐ No ☐

b. Date: ..... / ..... / ..... ***and*** Result: Normal ☐ Abnormal ☐

(Please attach a photocopy of any abnormal result)

3. Epileptic Seizures

a. Has the child had any other type of epileptic seizure since the last assessment? Yes ☐ No ☐

b. If **YES**, please give the type of seizure, with approximate frequency and duration of each type

.....

.....

4. Current drug treatment *(please record all drugs currently being taken)*

	Drug (i)	Total Daily Dose (ii)
a.		
b.		
c.		
d.		
e.		
f.		

Please turn over

5. Clinically important adverse events

a. Have the parents/guardians reported any clinically important adverse events (symptoms, illnesses or surgery) regardless of whether related to the treatment(s) given?

Yes ☐ No ☐

b. If **Yes**, please complete the details in the table below.
(If you think that the adverse event is attributable to the trial drug, please place an asterisk (*) in the first box.)

	Adverse event	Date of onset	Hospitalisation		Action taken				Clinical outcome		
			Yes	No	None	Treatment			Recovered	Not recovered	Unknown
						Reduced	Stopped	Stopped temporarily			
*											

6. Developmental history at time of this assessment

In your opinion, is the infant's development appropriate for age? Yes ☐ No ☐

7. Neurological assessment (excluding development)

a. Is the neurological examination of the infant currently normal? Yes ☐ No ☐

b. If **NO**, please describe any positive findings below:

8. *(i) Current weight: • kg (ii) Current head (occipitofrontal) circumference: • cm*

9. Investigations performed to find underlying cause

Have any further investigations been performed since the child's last review?
Please list and give the results where available

a)

b)

c)

d)

e)

10. Any other comments

11. *Is there a known underlying diagnosis/aetiology for this patient's spasms?*

Yes ☐ No ☐

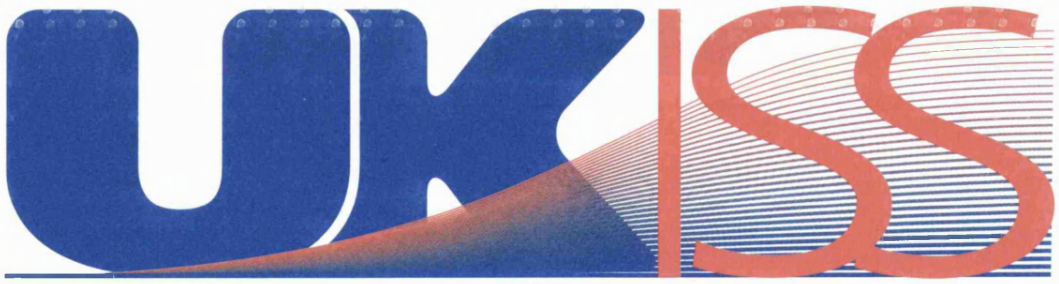
If **YES**, please comment:

Please send a photocopy of this completed form, together with the remaining pages of the Patient's Diary, to the Trial Centre (as in Action Plan 1, 2 or 3)

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park BATH BA1 3NG

Thank you very much for your help

Appendix 1



The United Kingdom Infantile Spasm Study

TRIAL PROTOCOL

PLEASE NOTE: As ACTH gel is not available in the UK, we have substituted Synacthen Depot.

Give 0.5mg on alternate days (equivalent to 40iu/day of ACTH) intramuscularly (regardless of age or weight) for two weeks. If at the end of the first week seizure control has not been achieved then the dose should be further increased to 0.75mg on alternate days (equivalent to 60iu/day of ACTH) intramuscularly.

Before prescribing Synacthen Depot, please read the Doctor's Information Sheet.

September 1998

Version 2 MREC Approved

5. Clinically important adverse events

a. Have the parents/guardians reported any clinically important adverse events (symptoms, illnesses or surgery) regardless of whether related to the treatment(s) given?

Yes ☐ No ☐

b. If **Yes**, please complete the details in the table below.
(If you think that the adverse event is attributable to the trial drug, please place an asterisk (*) in the first box.)

	Adverse event	Date of onset	Hospitalisation		Action taken				Clinical outcome		
			Yes	No	None	Treatment			Recovered	Not recovered	Unknown
						Reduced	Stopped	Stopped temporarily			
*											

6. Developmental history at time of this assessment

In your opinion, is the infant's development appropriate for age? Yes ☐ No ☐

7. Neurological assessment (excluding development)

a. Is the neurological examination of the infant currently normal? Yes ☐ No ☐

b. If **NO**, please describe any positive findings below:

.....

.....

8. *(i) Current weight: • kg (ii) Current head (occipitofrontal) circumference: • cm*

9. Investigations performed to find underlying cause

Have any further investigations been performed since the child's last review?
Please list and give the results where available

a) .....

b) .....

c) .....

d) .....

e) .....

10. Any other comments

.....

.....

.....

11. *Is there a known underlying diagnosis/aetiology for this patient's spasms?*

Yes ☐ No ☐

If **YES**, please comment: .....

.....

Please send a photocopy of this completed form, together with the remaining pages of the Patient's Diary, to the Trial Centre (as in Action Plan 1, 2 or 3)

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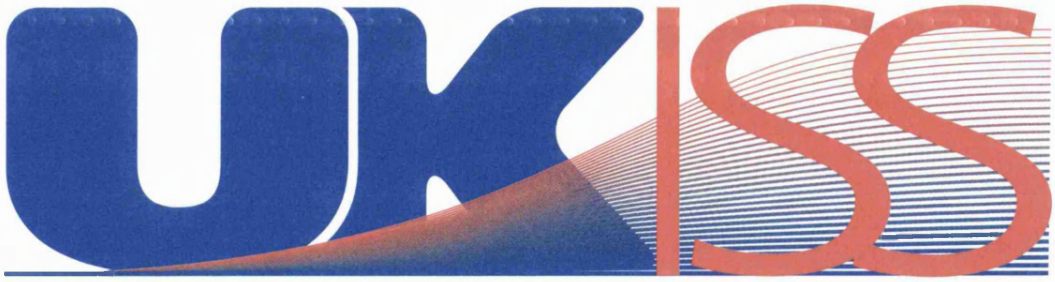
Royal United Hospital
Combe Park BATH BA1 3NG

Thank you very much for your help

Appendix 1



The United Kingdom Infantile Spasm Study

TRIAL PROTOCOL

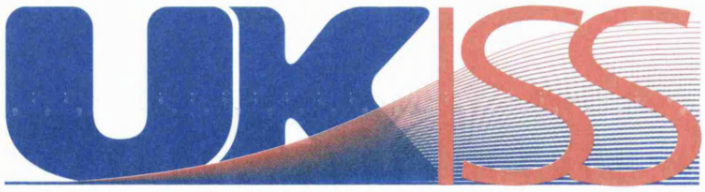
PLEASE NOTE: As ACTH gel is not available in the UK, we have substituted Synacthen Depot.

Give 0.5mg on alternate days (equivalent to 40iu/day of ACTH) intramuscularly (regardless of age or weight) for two weeks. If at the end of the first week seizure control has not been achieved then the dose should be further increased to 0.75mg on alternate days (equivalent to 60iu/day of ACTH) intramuscularly.

Before prescribing Synacthen Depot, please read the Doctor's Information Sheet.

September 1998

Version 2 MREC Approved



The United Kingdom Infantile Spasm Study

Trial Centre

The Children's Centre
Royal United Hospital
Combe Park
Bath BA1 3NG
Tel/Fax: 01225 824206

Trial Steering Committee

In Bath: Prof J P Osborne (Chairman)
Dr S Edwards
Dr E Hancock
Dr A Lux
Dr F O'Callaghan

Also: Dr T Johnson (MRC, Cambridge)
Dr C Kennedy (Southampton)
Dr R Newton (Manchester)
Dr C Verity (Cambridge)

RANDOMISATION

Telephone: 01225 824490 / Monday to Friday between
***or by* Facsimile: 01225 824206** \ 8.30am and 6pm only

Please report all cases, even if not for randomisation

Protocol Contents

The United Kingdom Infantile Spasm Study

PROTOCOL

This is a pragmatic drug trial of the current, most common treatments using the clinicians normal investigation plan.

EPIDEMIOLOGY

NOTIFY ALL CASES OF INFANTILE SPASMS

Please notify all cases of infantile spasms to the trial centre even if you do not intend to recruit the individual patient, for whatever reason, into the trial. Any patient with a clinical diagnosis of infantile spasms should be included even if the EEG turns out to be normal. This would include patients younger than 2 months or older than 1 year. It would be very helpful if all cases can be notified so that we know how representative our trial population is compared to the whole UK population. Brief clinical details will be requested.

In order to carry out a capture-recapture analysis of the UK population with IS (thus allowing a more complete ascertainment of cases), we shall ask for information from pharmacists and EEG departments in collaborating hospitals. This information will be initials , date of birth and sex. The clinician will then be approached for pre-randomisation stratification data.

DRUG TRIAL

1. INCLUSION CRITERIA FOR DRUG TRIAL

All infants shall be included of either sex aged at seizure onset between 2 completed calendar months and 1 year of age (up to but not including their first birthday) who are resident in the UK and who have a clinical diagnosis of infantile spasms from any cause.

2. EXCLUSION CRITERIA FOR DRUG TRIAL

(i) Infants who are either known to suffer from tuberous sclerosis (TSC) or who are at high risk i.e. a presumptive diagnosis of tuberous sclerosis because of:
(a) known affected parent
(b) previously diagnosed cardiac rhabdomyoma
(c) hypomelanic macules, a forehead fibrous plaque or shagreen patch noted
(d) a retinal phakoma seen
(e) polycystic kidneys in the infant

We recommend that first line therapy in these infants should be vigabatrin (see later for dosage. Please inform trial centre even though they will not be entered into the trial)

(ii) Infants previously treated with vigabatrin or steroids within 28 days of the first diagnosis of infantile spasms.
(iii) Infants with a contra-indication to vigabatrin or steroids.
(iv) Infants with a lethal or potentially lethal other condition.
(v) Previous treatment for infantile spasms.
(vi) Inability of parents or guardians to give informed, signed consent.
(vii) Infants expected to leave the UK within one month of randomisation.
(viii) Inability of parents or guardians to know when spasms stop - to the nearest whole day.
(ix) Infants enrolled in a concurrent trial that either uses therapy that might affect the outcome measures of the UKISS trial or one that is time/effort consuming for the patients/guardians or the infants' medical practitioners.

All excluded infants should be reported to the trial centre.

3. CONSENT

The trial should then be discussed with the parents or guardians and their consent requested for participation in the trial. Please report any infants where consent is not obtained to the trial centre.

4. ELECTROENCEPHALOGRAM (EEG)

An EEG (or video EEG) should be obtained as quickly as possible so that treatment can start within 72 hours of diagnosis. **Only** if this is not possible and **only** if your normal practice is to start treatment prior to an EEG (or video EEG) may you randomise before an EEG (or video EEG) is obtained. If the EEG (or video EEG) is normal, a sleep EEG will be required prior to randomisation, if this has not already occurred. If the sleep EEG is normal the child will be excluded from the drug trial (unless already enrolled) but please report the exclusion to the trial centre for further follow up.

If there will be a delay of more than 72 hours before the EEG (or video EEG) can be performed and it is **not** your normal practice to start treatment prior to EEG (or video EEG), the child will be excluded from the drug trial (but please report the exclusion to the trial centre for further follow up).

5. PRE-RANDOMISATION

Prior to entry into the study the children will be stratified for randomisation by three variables:

(1) ***By gender:*** male, female

(2) ***By age:*** 60 to 119 days
120 to 179 days
180 to 239 days
240 days and over

(3) ***By diagnosis known at time of randomisation*** (Yes / No).
A: a proven chromosomal abnormality
B: a proven syndrome diagnosis
C: a diagnosis of cerebral palsy made before the onset of the infantile spasms
D: a diagnosis of neonatal encephalopathy with seizures

E: a diagnosis of delayed development having already been made **before** the onset of the spasms. The diagnosis should have been made by either a medical practitioner or a health visitor, and **must have been made before the** onset of the spasms.

Stratification is being done not to provide definitive groups for subanalysis but to balance the treatment groups with respect to factors which are identifiable at randomisation and which might affect our outcome measures.

6. RANDOMISATION

This will involve central randomisation by telephone call which will register the child into the trial, report base-line information and allocate initial treatment using the method of minimisation balancing over three factors.

7. TREATMENT GROUPS

All children eligible for the trial will then be randomised into two treatment groups:

(1) Vigabatrin
(2) "Steroids"

All patients randomised to receive steroids will undergo a second randomisation at that time to either Synacthen Depot or prednisolone.

The only pharmacological intervention, for the infantile spasms, in the first two weeks will be the use of the drug to which each patient has been randomised.

8. INITIAL TREATMENT

This will be a period of two weeks during which the child will receive the drug to which they are allocated as monotherapy. It is the local doctor's responsibility to read the manufacturer's drug data sheet before prescribing the following drugs:

Vigabatrin

Give 50mg/kg/day orally in two divided doses for 24 hours (i.e. a total of 2 doses). Then increase to 100mg/kg/day orally in two divided doses in all patients.
If at 96 hours seizure control has not been achieved then the dose should be further increased to 150mg/kg/day orally in two divided doses.
They then continue on this dose (100 or 150mg/kg/day) until the time of their final developmental assessment around 12 - 14 months of age unless no response or relapse occurs (see below), or this is not your normal practice.

ACTH — USE SYNACTHEN DEPOT

As ACTH is not available in the UK, we have substituted Synacthen Depot. Give 0.5mg on alternate days (equivalent to 40iu/day of ACTH) intramusclarly (regardless of age or weight) for two weeks. If at the end of the first week seizure control has not been achieved then the dose should be further increased to 0.75mg on alternate days (equivalent to 60iu/day of ACTH) intramuscularly. *This group will then tail on oral prednisolone over 15 days.* Those on 0.5mg on alternate days of Synacthen Depot will receive 30mg of oral prednisolone for 5 days, then 20mg for 5 days then 10mg for 5 days and then stop. Those on 0.75mg of alternate days of Synacthen Depot will receive 40mg of oral prednisolone for 5 days then 20mg for 5 days and then 10mg for 5 days and then stop.

Prednisolone

Give 10mg q.d.s. orally (regardless of age or weight) for two weeks.
If at the end of the first week seizure control has not been achieved the dose should be increased to 20mg t.d.s. orally.

This group will then tail on oral prednisolone over 15 days. Those on 40mg will reduce to 30mg for 5 days, then 20mg for 5 days then 10mg for five days and stop. Those on 60mg will reduce to 40mg for 5 days then 20 mg for 5 days then 10mg for 5 days then stop.

9. INVESTIGATIONS

(a) An investigation of the child's development will be made by history. At enrolment the clinician will be asked to record the best development ever made on history by the child. It will not be necessary to record the age at which this performance was made. They will then be asked to record the current development achieved.

(b) As part of normal practice in the investigation of infants with infantile spasms, we assume the following investigations will be undertaken:

1. MRI or CT of the brain
2. Urine metabolic screen for amino acids
3. Ophthalmoscopy (either direct or indirect)
4. Ultraviolet light examination (Woods light)

The results of these tests should be forwarded to the trial centre. If for any reason one or more of these tests is not completed the reason should be stated.

(c) The following tests may be considered appropriate in some cases and, if performed, the results of these and any other tests should be forwarded to the trial centre.

1. Urea and electrolytes
2. Liver function tests
3. Chromosomes
4. Urine metabolic screen for organic acids
5. Lactate
6. Biotinidase assay
7. Ammonia
8. Thyroid function
9. Pyridoxine response - if pyridoxine is to be given we would recommend that pyridoxine is given one month after the start of the trial (after both the randomised treatment and first alternate treatment have been given in a child who continues fitting).

(d) When venesection is performed for any clinical reason during the course of the infants illness, please take a blood sample for DNA analysis (bottle, form and addressed sample box included in patient pack). A subgroup of those on steroids will have blood taken to measure cortisol levels.

10. INITIAL OBSERVATIONS

The patient will be admitted if necessary for clinical confirmation of the diagnosis of infantile spasms. If commencing steroid treatment, the patient will preferably be detained in hospital for 48 hours in order to have their blood pressure checked twice a day for two days and to have a urine analysis for glucose performed before discharge.

11. AT ENROLMENT

At enrolment the parents/guardians will be given their copy of a 'fit diary'. Its use, and how to complete it, must be explained and fully understood. In addition the importance of this diary to interpreting the results of the trial should be explained. Details of the

child's name, date of birth, address, NHS number, trial number, consultant and general practitioner should be completed. In addition we will ask all parents/guardians for a third party address (e.g. a grandparent) so that if they move and we lose contact with them we can try and track them through this third party.

As a minimum, the parents/guardians will be expected to make a once daily entry for the first 4 weeks of the trial and a once weekly entry thereafter, until the time of the final developmental assessment (12 -14 months), with a final 7 day daily entry for those still having seizures. They should bring the diary with them to all clinic appointments and they may use the diary to record more detailed information if the lead clinician so wishes.

12. BEFORE DISCHARGE

Before discharge please arrange for a follow up EEG as close to 14 days after the start of treatment as possible. Please also see the child in out-patients as close to 14 days after the start of treatment as possible (**but not less than** 14 days after the start of treatment).

13. FOLLOWING DISCHARGE, DURING THE INITIAL TWO WEEK PERIOD

Once the patient is discharged from hospital, if on steroids the blood pressure and urine analysis for glucose should be performed weekly whilst treatment continues, until the dose is reduced when this may be omitted if problems have not already been detected.

14. RESPONDERS AND PROPOSED TREATMENT FOR RELAPSE

Responders: are those in whom there is total cessation of spasms for at least 48 hours up to and including the end of the 14th day of treatment.

Relapse: a single spasm in a responder constitutes a relapse.

If a child relapses within the initial 2 week period then the lead clinician would be expected to increase the dose of the initial therapy up to the maximum recommended dose as per protocol.

If for any reason the lead clinician felt that it was not in the child's best interest to increase the dose of initial therapy (for example side effects experienced) then he should inform the trial centre as soon as possible, preferably but not necessarily before changing therapy.

15. REVIEW AT 2 WEEKS

Please review the patient as close to 14 days after the start of treatment as possible but not less than 14 days after the start of treatment.

The patient should be seen in order to confirm their progress and to complete the brief standardised progress report form. If the infant has responded the patient will continue on the same therapy as above.

16. NON - RESPONSE AT 2 WEEKS

The trial will be analysed by intention to treat at randomisation. However, in order to minimise the effects of a multitude of different subsequent treatments, we will ask, but not require, clinicians to change to the alternative treatment if the primary treatment fails.

If a response has not occurred after 2 weeks, we expect the lead clinician to change to the alternative therapy i.e. either steroids after vigabatrin (the lead clinician to choose which steroid – Synacthen Depot or prednisolone) or vigabatrin after steroids. This alternative treatment will continue for the third and fourth weeks (a full 14 days) at the same dose as recommended for the first two weeks.

If the lead clinician does not feel that this treatment is in the child's best interest they may change to a treatment of his/her own choice, without violating the trial protocol, but they should notify the trial centre of this change in treatment plan using the 14 day standard report form.

If both treatments fail, the clinician will be left to choose the most appropriate treatment.

17. RELAPSE AFTER THE INITIAL TWO WEEK PERIOD

The lead clinician may choose his/her own treatment, but we suggest; if the child relapses after the initial two week period either: **If on vigabatrin** increase the dose in parallel with the child's weight gain (if increase is more than 1 kg) or if on 100mg/kg/day increase to 150mg/kg/day; **If on steroids** repeat the course **once** even if tailing. If these measures fail after a full 14 days treatment change to the alternative therapy i.e. either steroids (Synacthen Depot or prednisolone) after vigabatrin, or vigabatrin after steroids.

18. SIDE EFFECTS

Should an infant suffer unacceptable side effects then the treatment should be discontinued and the trial centre informed immediately. The lead clinician may choose his own alternative treatment but we suggest, the lead clinician change to the alternative therapy i.e. either steroids (Synacthen Depot or prednisolone) after vigabatrin, or vigabatrin after steroids.

19. SUBSEQUENT FOLLOW UP

1. All enrolled infants should be seen at 3 monthly intervals as a minimum although we realise that many will be seen more often because of their clinical need. The lead clinician will be asked to fill in a brief progress report form to send back to the trial centre in Bath at each 3 monthly visit until the 12 - 14 month assessment.

2. Psychomotor development will also be assessed using a telephone questionnaire based on the "Vineland Adaptive Behaviour Scales" (see Section 26). This will be done by a trained researcher who will be based in Bath when the infant is between 12 and 14 months of age.

20. RECRUITMENT RATE

This is a national study and it is hoped to recruit all new cases of infantile spasms in the United Kingdom occurring within the study period. Papers dealing with the epidemiology of infantile spasms put the incidence between 1 in 2380 and 1 in 6250 births. The average UK birth rate is approximately 800,000 per year. Therefore, it should be possible to recruit between 130 and 340 new cases per year. Taking into account exclusions, recruitment should be completed within 18 months.

We intend to drive recruitment actively and have already sought to recruit one paediatric neurologist from each old health region to help promote the study. The trial centre will take responsibility for ethics committee approval for each district in the UK and will recruit one paediatrician from each district to help promote the study. We will provide coasters and Post-it notes printed with contact arrangements at the commencement of

the trial. A newsletter will be sent out to all recruiting clinicians and all promoters every two months.

We will notify all EEG departments of the trial with coasters, post-its and newsletters and ask them to remind clinicians of the trial whenever a request is made for an EEG in a child with possible infantile spasms, or whenever hypsarrhythmia is found.

21. COMPLIANCE

This is a serious disorder with profound sequelae. The motivation for clinicians and parents of patients to participate in treatment is high. The clinical workload to be imposed on attending physicians is little more than constitutes good clinical practice. (The workload to be imposed on parents is small.) The administrative work will be kept to a minimum. We will not collect unessential data and the trial centre will be responsible for documentation and for submissions to ethics committees.

22. LIKELY RATE OF LOSS TO FOLLOW-UP

Loss to follow-up should be small. Patients known to be likely to move outside the country during the trial period will be excluded at entry. As this is a national study, movement within the UK should not lead to loss of contact. Patient's NHS number, general practitioner and a third party address (e.g. grandparents) will be recorded on entry to the trial thus making it easier to keep track of patients who move.

23. POST RANDOMISATION STRATIFICATION

There will be post-randomisation stratification for potential confounding variables not accounted for in pre-randomisation. These include EEG appearance (i.e. hypsarrhythmia vs atypical vs normal awake, normal asleep) and diagnostic sub-groups (i.e. cerebral dysgenesis on cranial scanning, chromosomal abnormalities or other syndromes and other diagnosis such as metabolic disease).

Social factors will include birth order and maternal age at school leaving.

24. POST INVESTIGATION DIAGNOSTIC SUB GROUPS

It may be possible to see if any trends in outcome are repeated within subgroups of the trial population.

The largest subgroup should be infants where development was delayed (as shown by pre-randomisation stratification data and, separately, by development history).

Smaller subgroups, e.g. those diagnosed with cerebral palsy on clinical examination, cerebral dysgenesis on cranial imaging, normal awake and asleep EEGs, are unlikely to be large enough for separate analysis. However, the data will be examined in case there is a dramatic difference in outcome, or a consistent trend.

25. PRIMARY OUTCOME MEASURE

The primary outcome measure will be the number of patients who achieve complete cessation of spasms for at least 48 hours up to and including the end of the 14th day of treatment.

26. SECONDARY OUTCOME MEASURES

1. Time taken to complete cessation of all spasms for at least 48 hours.
2. Partial response i.e. those patients that have a reduction in the number of spasms during the two week period.
3. Relapse rates.
4. Other seizure types and frequency at 14 months, in those still having seizures.
5. Resolution of hypsarrhythmia at 14 days.
6. Developmental progress at 12 -14 months of age. This will allow at least 2 months of recovery following treatment and is an age at which some language development has occurred. It is believed that delaying the assessment to a greater age will give little advantage and would have the disadvantage of increasing the impact of environmental factors.

The Vineland Adaptive Behaviour Scales have been developed and validated in the U.S.A. to measure "adaptive behaviour" defined as the performance of the daily activities required for personal and social sufficiency. It concentrates on the usual response, not the best response to any task. It has been validated in greater detail on larger numbers of children (3000) and has been used in the U.K. for other developmental follow-up studies. It achieves construct validity, content validity and has been compared to other scales in both normal and handicapped children. It has been shown to have internal consistency, test-retest and interrater reliability. It has been designed to minimise the influence of physical handicap.

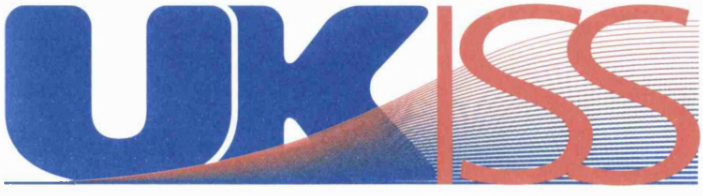
The Vineland has four domains (communication, daily living skills, socialization and motor skills) and these combine to give an Adaptive Behaviour Composite: each of these has a standard score of 100 with a standard deviation of 15 and each can be expressed as an age equivalent (developmental age).

The Vineland scales can easily be adapted to be performed as a parental questionnaire that can be administered over the phone.

27. ANALYSIS

Assuming recruitment of 250 children over the 18 month period, with approximately 125 randomised to vigabatrin and 125 to "steroids" and, assuming approximately 50% will achieve cessation of seizures in the "steroid" group, the trial will have 90% power to detect an improvement in cessation of seizures to 70% in the vigabatrin group.

We are aware that the pattern of developmental age in the two groups may be bimodal. A direct comparison of the developmental age (total score and subsets) of the two groups will be undertaken, but we will also determine the proportion of individuals in each group whose development is one, two and three standard deviations below the mean for the Vineland.



The United Kingdom Infantile Spasm Study
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01367

The United Kingdom Infantile Spasm Study

PATIENT'S DIARY

Name: .....

Address: .....

.....

.....

Study number:

Your consultant doctor's team can be contacted by phoning .....

and asking for .....

NOTE TO DOCTOR: Please photocopy completed pages before posting and keep original for yourself. The original will be needed if the copies are lost in the post

Introduction to the Patient's Diary

Thank you for agreeing to take part in the UKISS study which will help us find out more about infantile spasms. This diary will be a record of your child's spasms and other important information.

How to use your diary — for the first 2 weeks

1. Please fill in your child's name and address on the front of this diary. Please make sure that your doctor fills in the study number and how to contact him or her.
2. Please fill in your **child's name** and **study number** on **EACH PAGE** of this diary.
3. Please fill in pages **D3** to **D5** and start page **D6** ***as soon as*** *you are* given the diary, which must be before your child starts treatment.
4. During the first two weeks of treatment we need to know what happens to your child's spasms. Please fill in the details about the number of batches and the number of spasms per batch as best you can. Please write ***'none'*** if your child has no spasms on a particular day. We want to find out when the spasms stop. We also want to know if the spasms come back.
5. We are interested in side effects or problems with the treatment; things such as vomiting, rashes, or excessive sleepiness.
6. We have left room for you to write details about other illnesses that your child may have and anything else that you think might be important. Please write as much as you like.
7. At the end of the first two weeks of treatment you will be seeing your doctor again. This should be as close to 14 days after the start of treatment as possible - but not less than 14 days. At this visit, please ask your doctor to photocopy pages **D3, D4, D5, and D6** of this diary and then forward them to us.
8. Remember: it is **important** that **YOUR CHILD'S NAME AND STUDY NUMBER ARE ON EACH PAGE**. Please check this now.
9. **If your child has only one spasm at a time** and never has batches of spasms, please take great care when filling in the tables on the following pages. Put the number of single spasms occuring during one day (midnight to midnight) in the column headed ***"number of batches"*** and change the word ***"batches"*** in this heading to ***"spasms"***. The correct response to the question ***"maximum (largest) number of spasms in one batch this day"*** would be ***"one"***.

Thank you for helping us to get this information

01367

Child's Name: UKISS Study Number:

Questionnaire for infantile spasms

Please fill out pages **D3, D4 and D5** *as soon as you can. This will give us useful information about your child's illness before the treatment started. Your doctor will ask to see this when he /she next sees you. If you do not understand any of the questions then ask your doctor.*

Your child's name: .....

Date of Birth: ..... / ..... / ..... (day/month/year)

NHS number (if known) .....

Please give us the name and address of a friend, or someone in your family, who would be able to forward letters to you if you move house or if we do not know where you are.

Name: .....

Address: .....

.....

.....

GENERAL DESCRIPTION OF SPASMS

1. Please tell us what happens when your child has a spasm *(please use your own words)*.

.....

.....

.....

.....

.....

.....

.....

2. Do the spasms ever occur one at a time or do they occur in batches (ie several at one time)? *(Please tick (✓) one of the following)*

only one spasm at a time ☐

only in batches of spasms ☐

sometimes one spasm at a time, and sometimes batches ☐

01367

Child's Name: UKISS Study Number:

HOW OFTEN IS YOUR CHILD HAVING INFANTILE SPASMS?

*A **batch** of spasms is when two or more spasms occur in a short space of time.*

*3. Number of **BATCHES** occurring in one day ...*

On average, how many **BATCHES** occur in a period lasting from midnight one day to midnight the following day? Please tick (✓) below for an **average day** during the past week, or since the spasms began if this is less than 7 days ago. *(please tick (✓) one)*

5 or fewer ☐ *6 to 10* ☐ *11 to 20* ☐ *21 to 40* ☐ *More than 40* ☐

Again, but **for the worst day**, how many **BATCHES** occur in a period lasting from midnight one day to midnight the next day? Please tick (✓) below for the **worst day** (ie the day with the most batches) during the past week. *(please tick (✓) one)*

5 or fewer ☐ *6 to 10* ☐ *11 to 20* ☐ *21 to 40* ☐ *More than 40* ☐

Again, but **for the best day**, how many **BATCHES** occur in a period lasting from midnight one day to midnight of the next day? Please tick (✓) below for the **best day** (ie the day with the smallest number of batches) during the past week. (If the spasms started less than 7 days ago, only include days after the spasms started.) *(please tick (✓) one)*

5 or fewer ☐ *6 to 10* ☐ *11 to 20* ☐ *21 to 40* ☐ *More than 40* ☐

*4. Number of **SPASMS** occurring **during any one batch***

During the past week (or since the spasms started if this is less than 7 days ago), how many spasms occurred, **on average**, during one batch? *(please tick (✓) one)*

5 or fewer ☐ *6 to 10* ☐ *11 to 20* ☐ *21 to 40* ☐ *41 to 80* ☐ *More than 80* ☐

During the past week, what is the **MAXIMUM (largest) number of spasms** that have occurred during one batch? *(please tick (✓) one)*

5 or fewer ☐ *6 to 10* ☐ *11 to 20* ☐ *21 to 40* ☐ *41 to 80* ☐ *More than 80* ☐

During the past week (or since the spasms started if this is less than 7 days ago), what is the **MINIMUM (smallest) number of spasms** that have occurred during one batch? *(please tick (✓) one)*

5 or fewer ☐ *6 to 10* ☐ *11 to 20* ☐ *21 to 40* ☐ *41 to 80* ☐ *More than 80* ☐

01367

Child's Name: UKISS Study Number:

Movements of the body during an attack

5. The spasm involves the following **movements of parts of the body.** *(Please record the direction of the **fastest** or strongest movement) (please tick (✓) 'Yes' or 'No')*

The **head** moving forwards Yes ☐ No ☐

The **head** moving backwards Yes ☐ No ☐

The **eyes** moving sideways Yes ☐ No ☐

if **Yes,** To one side only ☐ **or** to both sides ☐

The **trunk** (body) moving forwards Yes ☐ No ☐

The **trunk** (body) moving backwards Yes ☐ No ☐

The **arms** Yes ☐ No ☐

if **Yes,** Left arm only ☐ **or** right arm only ☐ **or** both arms ☐

The arms bend in towards the chest Yes ☐ No ☐

The arms are flung out, away from the body Yes ☐ No ☐

The **legs** Yes ☐ No ☐

if **Yes,** Left leg only ☐ **or** right leg only ☐ **or** both legs ☐

Leg(s) bend and are brought up to the body Yes ☐ No ☐

Leg(s) straighten out, away from the body Yes ☐ No ☐

Timing of spasms

6. Do the spasms occur at any particular time? Yes ☐ No ☐

if **Yes,** *(please tick (✓) one or more)*

morning ☐ afternoon ☐ evening ☐ night-time ☐

other ☐ *please specify:* _____

Have you noticed anything that sets the spasms off? *Yes* ☐ *No* ☐

if **Yes** *Please specify:* _____

_____

_____

and does it trigger the spasm ...

always ☐ usually ☐ sometimes ☐ *(please tick(✓)one)*

01367

Child's Name: UKISS Study Number:

INITIAL TREATMENT

Name of treatment: .....

Please use this page of your diary to keep a daily record of your child's spasms during the first two weeks of the study.

Date treatment started: ___/___/___ **YOU MUST FILL IN THIS DATE**

DAILY	Number of **batches*** in a day. (midnight to midnight)	Maximum (largest) number of **spasms** in one batch this day	Please tick here if any treatment missed
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			

* (or number of single spasms if they do not occur in batches)

Please record in the table below anything else that you think may be important for the doctors running the trial to know: for example, unusual reactions that may be caused by the treatment, other illnesses, other medicines that have been started.

Date	
Date	
Date	
Date	
Date	
Date	

Please ask your doctor to photocopy pages **D3** to **D6** when they are completed and he/she will post the photocopy to us.

CHECKED BY Dr.: ..... **on:** ___/___/___

How to use your diary — after the first two weeks of the study

1. Please fill out the diary **daily** for a further two weeks.
2. For all children in the study, we will then need to keep a **weekly** record of progress until the time of the final study assessment at between 12 and 14 months of age.
3. Each time you visit your doctor, please let them see the diary. This will give you a chance to discuss it with them. Your doctor will send photocopies of the completed pages to us.
4. We will ask you to write down the number and type of fits for a week (7 days) after your child's first birthday. We want to know if your child continues to have spasms or develops any other form of fits.

If you would like to keep a copy of this diary, please ask your doctor to provide you with a photocopy. He/she will keep the original at the end of the study.

01367

Child's Name: UKISS Study Number:

SECOND TWO-WEEK PERIOD:

Name of treatment: .....

Please use this page of the diary to keep a daily record of your child's spasms during the second two-week period of the study.

Date 2nd treatment started: ..../..../.... **YOU MUST FILL IN THIS DATE** if your child has started a second treatment

DAILY	Number of **batches*** in a day. (midnight to midnight)	Maximum (largest) number of **spasms** in one batch this day	Please tick here if any treatment missed
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			
Date			

* (or number of single spasms if they do not occur in batches)

Please record in the table below anything else that you think may be important for the doctors running the trial to know: for example, unusual reactions that may be caused by the treatment, other illnesses, other medicines that have been started.

Date	
Date	
Date	
Date	
Date	
Date	

Please ask your doctor to photocopy this page at the end of two weeks and he/she will post the photocopy to us.

CHECKED BY Dr.: ..... **on:** ..../..../....

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Child's Name: UKISS Study Number:

GENERAL PROGRESS:

Once your child has finished the two (or four) weeks of treatment, please fill in the diary below ***once weekly*** *until they have their final study assessment at between 12 and 14 months of age. Please record the number of batches during the worst day that week and the number of spasms in the* ***longest*** *batch during that week. As before, record in the second table any information that you think will be useful for the doctors conducting the study to know about.*

WEEKLY	Number of **batches*** during the worst day (midnight to midnight) of this week	Maximum (largest) number of **spasms** in one batch
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		

* (or number of single spasms if they do not occur in batches)

Please record in the table below anything else that you think may be important for the doctors running the trial to know: for example, unusual reactions that may be caused by the treatment, other illnesses, other medicines that have been started.

Date	
Date	
Date	
Date	
Date	
Date	

Please ask your doctor to photocopy this page at the next visit and he/she will post the photocopy to us.

CHECKED BY Dr.: ..... **on:** ... / ... /

01367

Child's Name: UKISS Study Number:

GENERAL PROGRESS *(continuation sheet)*

*If you have completed the table on page **D9**, please fill in the diary below **once weekly** until your child has their final study assessment at between 12 and 14 months of age. Please record the number of batches during the worst day that week and the number of spasms in the longest batch during that week.*

WEEKLY	Number of **batches*** during the worst day (midnight to midnight) of this week	Maximum (largest) number of **spasms** in one batch
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		
Date		

* (or number of single spasms if they do not occur in batches)

Please record in the table below anything else that you think may be important for the doctors running the trial to know: for example, unusual reactions that may be caused by the treatment, other illnesses, other medicines that have been started.

Date	
Date	
Date	
Date	
Date	
Date	

Please ask your doctor to photocopy this page at the next visit and he/she will post the photocopy to us.

CHECKED BY Dr.: ..... **on:** ..../..../....

01367

Child's Name: UKISS Study Number:

CONTINUING FITS

Please complete this page after your child's 1st birthday.

Please make a **daily entry for one week**. Please fill in the types of fits that your child is having and the number they have each day. If they are having more than one type of fit, please record the number of each type that they are having. If you are not sure what type of fits your child is having you should ask your doctor.

Date	Type of fit	Number of fits this day
Day 1		
Day 2		
Day 3		
Day 4		
Day 5		
Day 6		
Day 7		

or My child has not had any fit (epileptic seizure or spasm) during the past week. ☐

Signed: .....

Thank you very much for all your help.

If you have any questions about the study please contact your consultant doctor's team by telephoning the number on the front of this diary.

The UKISS Trial Centre
The Children's Centre
Royal United Hospital
Combe Park
BATH BA1 3NG